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EDITORIAL

Eye Movement Research in the Twenty-First Century—a Window to the Brain, Mind, and More

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Abstract

The study of eye movements not only addresses debilitating neuro-ophthalmological problems but has become an essential tool of basic neuroscience research. Eye movements are a classic way to evaluate brain function—traditionally in disorders affecting the brainstem and cerebellum. Abnormalities of eye movements have localizing value and help narrow the differential diagnosis of complex neurological problems. More recently, using sophisticated behavioral paradigms, measurement of eye movements has also been applied to disorders of the thalamus, basal ganglia, and cerebral cortex. Moreover, in contemporary neuroscience, eye movements play a key role in understanding cognition, behavior, and disorders of the mind. Examples include applications to higher-level decision-making processes as in neuroeconomics and psychiatric and cognitive disorders such as schizophrenia and autism. Eye movements have become valued as objective biomarkers to monitor the natural progression of disease and the effects of therapies. As specific genetic defects are identified for many neurological disorders, ocular motor function often becomes the cornerstone of phenotypic classification and differential diagnosis. Here, we introduce other important applications of eye movement research, including understanding movement disorders affecting the head and limbs. We also emphasize the need to develop standardized test batteries for eye movements of all types including the vestibulo-ocular responses. The evaluation and treatment of patients with cerebellar ataxia are particularly amenable to such an approach.

Keywords Saccade · Vestibulo-ocular reflex · Pursuit

Eye movements are critical for the survival of any animal that sees. Promptly bringing an image to the fovea of an object that suddenly intrudes into one's periphery, and then keeping the image stable on the fovea, allows the cognitive brain to analyze the visual scene in a tenth of a second. In this way, it can generate an immediate, and sometimes life or death, decision whether to flee, fight, embrace, or just do nothing. Neural correlates of eye movements are found in almost every corner of the brain, helping to provide the most reliable information from our visual systems for all aspects of behavior.

Using eye movements to understand human disease extends back to at least the mid-nineteenth century when early reports of strabismus [1–5] and nystagmus [4, 6–13] appeared. Nevertheless, in the years following, for almost another century, the literature on eye movements was meager. In the mid-1940s, however, the number of publications on nystagmus and strabismus began to grow (https://www.ncbi.nlm.nih.gov/pubmed/?term = nystagmus, https://www.ncbi.nlm.nih.gov/pubmed/?term = strabismus), and in the mid-1960s, there was another growth spurt with more studies reporting various types of dysfunction of eye movements in conditions affecting the brainstem or cerebellum. Topics such as adaptive control of eye movements and the central role of normal and

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abnormal vestibulo-ocular responses in revealing mechanisms underlying the control of eye movements of all types also began to receive special emphasis (Fig. 1) (https://www.ncbi.nlm.nih.gov/pubmed/?term=nystagmus, https://www.ncbi.nlm.nih.gov/pubmed/?term=strabismus, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+brainstem, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+ataxia, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+motor+adaptation, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+vestibulo-ocular+reflex).

The 1960s became a watershed in ocular motor research for both technical and conceptual reasons. The magnetic field search coil method for measuring eye movements was a boon for ocular motor research in both humans and experimental animals. It gives accurate, sensitive, reliable measures of the position of the eye around all three axes of rotation. This methodology, combined with the new techniques of recording of activity from single neurons in alert behaving animals, made possible precise correlations between behavior and neural activity. New anatomical tracing techniques also helped to unravel the connectivity of the circuits that showed activity related to eye movements [14–17]. The effects of microinjections of chemicals that mimic normal neurotransmitters, focal electrical stimulation, and naturally occurring experimental lesions in the brain improved our understanding of brain function [18–31]. Conceptually, bioengineering approaches, using systems analytical techniques, were combined with anatomical and physiological data, to develop biologically plausible models, replacing the "black box" approach to neural modeling. The involvement of bioengineers in eye movement research, exemplified by David A Robinson, enticed basic and clinical neuroscientists to adopt the "engineering approach" to understanding normal brain function and human disease [27, 32–47].

Beginning in the1960s, clinical ocular motor research largely focused on the disorders of the cerebellum, brainstem, and orbit. Key information came from studies of the physical properties of the "oculomotor plant," the mechanical characteristics of the orbital contents that dictate what premotor commands were needed to move the eyes quickly to a new position and then to hold them there [48, 49]. Furthermore, largely based on studies in animals with experimental lesions and on patients with naturally occurring disorders of eye movements, the motor machinery in the brainstem and cerebellum that generated the requisite premotor commands was becoming relatively well understood. Consequently, eye movements became a powerful tool to measure motor function objectively in patients with neurological disorders and more generally as "a window to the workings of the brain." There were several critical insights relating basic physiology and anatomy to behavior. They included (1) the concept of a neural network performing mathematical integration of eye velocity to eye position (neural integration) for steady gaze holding and (2) the use of internal models based on efference copy and internal feedback that enable the brain to predict and when necessary correct its motor commands. This capability functions both as part of immediate, on-line control of each individual movement and long-term adaptive control as part of motor learning and calibration. Note that many of these functions and concepts depend upon activity in the cerebellum, both directly and through its connections to the brainstem and higher-level structures.

More recently, eye movements have assumed another key role in neuroscience, as quantitative markers of higher-level aspects of behavior. Many studies that focus on cognitive and behavioral neuroscience—for example, reward, attention, planning, and prediction—and disorders, such as autism, schizophrenia, and neglect, use eye movements as a "read out" of what the brain is planning, mulling over, or excited about (Fig. 1) (https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+biomarker, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+cognition, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+autism, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+cerebral+cortex, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+psychology, https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+behavior). The slope of this growth in publications has increased even more in the last decade (Fig. 1). Not only the eyes are windows to the brain but they have become windows to the mind. As many new therapies for neurological and psychiatric diseases have emerged, eye movements have become the biomarker exemplar, easy to measure and easy to quantify (https://www.ncbi.nlm.nih.gov/pubmed/?term=eye+movement+biomarker). In the case of spinocerebellar ataxia type 6 (SCA6), for example, the amplitude of the vestibulo-ocular reflex (gain) is initially high due to a loss of the inhibition from Purkinje cells upon the vestibular nuclei but eventually, the gain becomes low as the disease progressively involves the vestibular nuclei in the brainstem.

The abrupt growth of the biomarker and behavioral literature using eye movements is also related to technical advances and, especially, the invention of portable, non-invasive, and cost-effective eye trackers. In the late 1900s, eye movement research required a cumbersome and costly infrastructure, and highly trained investigators for acquisition, analysis, and interpretation of eye movement data. In contrast, contemporary off-the-shelf systems neither require sophisticated expertise to establish an eye movement laboratory nor mandate extensive training in interpreting and analyzing the eye movement data. All information is available from preconfigured algorithms built into the manufacturer-provided software. Many of these systems are portable and easy to use at the bedside. Nevertheless, caution is required. All methods of recording and analyzing eye movements are susceptible to artifacts from

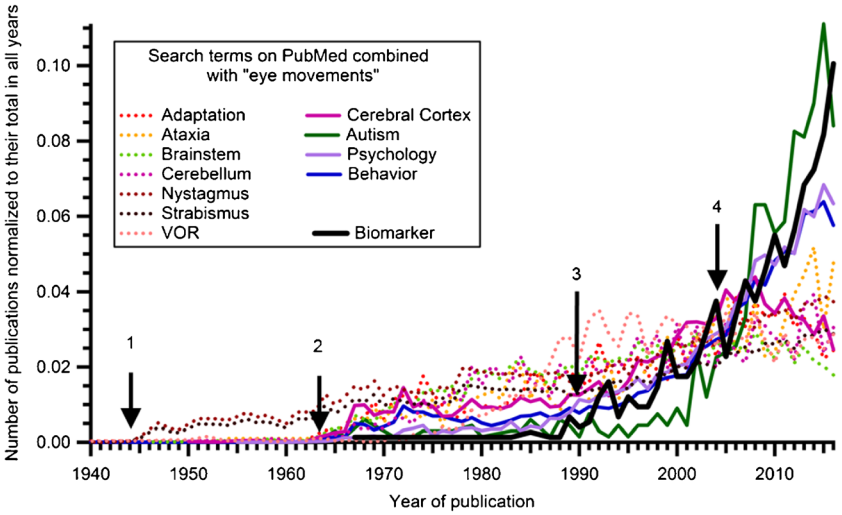

Fig. 1 Number of publications normalized to their total in all years and corresponding year of publication. The normalization compares relative frequency of published literature on a given topic. In the mid-1940s, there was increase in publications about nystagmus and strabismus (arrow 1); in the mid-1960s, there was increase in publication frequency reporting cerebellar or brainstem eye movement deficits (arrow 2). Arrow 3 depicts the start of increasing numbers of publication on cognitive function and then a further increase in literature in this category (arrow 4). Today, there are more publications using eye movements to study cognitive function than all publications on eye movements and cerebellar ocular motor function

the recording techniques themselves, from limitations in the computer analysis algorithms and unwanted fluctuations or noncompliance in the behavioral state of the subject or patient, which prevents them from properly performing the task.

What does this all mean to scientists and clinicians focusing on the function of the cerebellum and its diseases? We know more about the function of the cerebellum in the control of eye movements than on any other motor behavior. We know more about the anatomical substrate and compartmentalization within the cerebellum on eye movements than on any other motor behavior. We can record, quantify and interpret the effects of cerebellar lesions on eye movements better than on any other motor behavior. Taken together, eye movements become an ideal tool to probe both function and malfunction of the cerebellum. Consider saccades for example, inaccurate saccades—saccade dysmetria—is a hallmark feature of dysfunction of the dorsal cerebellar vermis and its underlying projection site, the posterior fastigial nucleus (saccade hypermetria) [30, 31, 50]. Other types of eye movements also show patterns of abnormality that localize to the cerebellum, gaze-evoked and downbeating nystagmus and impaired pursuit with the head still or moving point to the flocculus/parafloccculus, and periodic alternating nystagmus and impaired tilt suppression of post rotatory nystagmus to the nodulus [47]. Even finer distinctions can be made between the effects of lesions in small but adjacent structures within the cerebellum, for example, the flocculus versus the parafloccculus (tonsil) [18, 19, 26, 27, 29, 51, 52]. While not as well localized within the cerebellum, certain patterns of ocular misalignment strongly suggest cerebellar dysfunction (e.g., horizontal (eso, convergent) deviations of the eyes for distance viewing and vertical misalignment that alternates sense (which eye is higher) depending on right versus left gaze) [20, 53–59].

Similarly, eye movements and saccades in particular can be used to probe the functions of many other areas within the brain including within the thalamus, basal ganglia, and cerebral cortex. New behavioral paradigms have applications both in basic neuroscience research and many neurological and psychiatric disorders. They include (1) the antisaccade test (can the patient suppress a saccade to a target to a suddenly appearing in the visual periphery and instead generate a saccade to its opposite mirror location?), (2) the go no-go paradigm (when can the decision to make a saccade be revoked?), and (3) predictive tracking (can the patient anticipate the location of a target moving in a periodic fashion?). Inferring functions of the cerebellum based on behavior is particularly confounding because of the extensive interconnections and reciprocal influences between the cerebellum, brainstem, and the cerebral hemispheres. Nevertheless, carefully designed experiments using innovative testing paradigms can help tease out both normal and abnormal function. Novel imaging approaches too, anatomical, functional, and biochemical, paired with sophisticated behavior paradigms are boon to eye movement research. Using MRI spectroscopy, the performance during eye movement tasks can be correlated to the activity of specific neurotransmitters such as dopamine [60], GABA [61], or acetylcholine [62]. A combination of normal eye movement behavior with diffuse MRI-based tractography has revealed the cortical nodes associated with central activity related to motor programming needed to initiate movement [63]. Antisaccade performance in elderly patients has become

a valuable predictor for their performance on executive function tasks [64]. In Parkinson's disease, ocular motor behavior, quantitative volumetry of gray and white matters in the cerebral hemispheres, and executive function capabilities are well correlated [65]. There is a direct correlation between the latency for vertical antisaccades and atrophy of caudate, left inferior parietal lobule, and left frontal gyrus [66]. Transcranial magnetic stimulation (TMS), another high-temporal resolution technique, can interrupt saccades at different time points during their generation. Such studies can trace the flow of information through different parts of the brain from activation by a stimulus to the programming of the movement to the execution of the saccade itself [67–69].

What is needed now? Perhaps first is that neurologists become more aware of how eye movements can be used in their clinics, for diagnosis, monitoring of therapies, and clinical and basic research. A careful clinical bedside evaluation, using only visual inspection, of each of the major subtypes of eye movements—saccades, pursuit, gaze holding, vestibular responses, and alignment and vergence—takes only a few minutes and provides much useful information toward accurate diagnosis. Specific patterns of abnormalities often provide key localizing information. When eye movements are used as biomarkers or for basic research, quantitative recording techniques become necessary. Another critical goal is to develop and validate standardized testing batteries among laboratories [70]. A key aspect of cerebellar motor control, infrequently used as a biomarker, is the ability to undergo ocular motor adaptation, a core function of what David Robinson called "the cerebellar repair shop." As we make progress in the pharmacotherapy of neurodegenerative conditions and disease-modifying agents in the twenty-first century, it will become increasingly critical to define biomarkers that can track the evolution of cerebellar function. The eye movements can be precise and quantitative biomarkers to measure the effects of the novel pharmacotherapy on the cerebellar function. The motor tasks such as saccades, pursuit, gaze holding, vestibular ocular reflex, and vestibular ocular reflex cancelation can be objective biomarkers to measure the effects of pharmacotherapy on cerebellar motor function. Measure of cerebellar motor learning using saccade adaptation, pursuit adaptation, and vestibular ocular reflex adaptation can quantify the effects of pharmacotherapy on early or preclinical cerebellar disorders. Saccade adaptation occurs over short and long timescales. Cerebellar deficit results in impairment in shorter timescale while olivo-cerebellar dysfunction affects both timescales [71, 72]. Effects of pharmacotherapy on saccade adaptation task will be able to distinctly identify the cerebellar influence. Finally, non-motor ocular motor tests, such as antisaccade, memory-guided saccades, and go no-go task may allow objective measure of pharmacotherapy on the non-motor domain of the cerebellar function.

Currently, there are limited options for the pharmacotherapy of nystagmus and other gaze holding disorders. Classic literature has suggested baclofen as a treatment of cerebellar nystagmus, primarily the downbeat and periodic alternating

Table 1 Why should we study eye movements?

Wide representation in the brain	Virtually, every area of the brain has neurons with activity related to some aspect of ocular motor control.
Accessible	Eye movements are easy to elicit, measure, and quantify. The task has become even easier with the availability of easy to use, off-the-shelf portable eye trackers.
Well-known physiology	Ocular motor physiology is divided into a recognizable hierarchy with specific physiological properties and anatomical substrates.
Objectiveness	Eye movement experiments are amenable to the rigor of mathematical and computational approaches.
Common methodological interface	Eye movement experiments are easily combined with other methods (e.g., functional magnetic resonance imaging (fMRI), magneto-electroencephalography (MEG), transcranial magnetic stimulation (TMS)) to pinpoint and follow the flow of information through the brain as different behaviors are elaborated.
Inter-species comparison	Saccades are easily measured in experimental animal models from monkeys to mice to pigeons to frogs to goldfish to zebra fish.
Common professional interface	Clinicians (neurologists, psychiatrists, otolaryngologists, ophthalmologists) psychologists, bioengineers, basic neurophysiologists, and pharmacologists, all use saccades to assay brain functions.
Biomarkers	Eye movements are useful biomarkers in neurological and psychiatric disease, development and aging, personality traits and talents, rapidly fluctuating states of neurological function, and genetic phenotyping.
Convenience	Eye movements are convenient for studying cognition including prediction, memory, reward and attribution of value, attention, decision-making, impulsivity, learning and adaptation, and boredom.
Mechanics	For motor control scientists, saccades are especially attractive since eye muscles lack a stretch reflex and move their effector (the globe) around a single axis (one joint).
Hypothetical extension	Relating the behavior of saccades to neurotransmitters, ion channel functions, membrane kinetics, and neural circuitry is relatively easy.
Translation from bench-to-bedside	Knowledge about saccades is easily translated into clinical diagnosis and treatment. Study of patients with disorders of saccades has led to major discoveries about how the brain works.

nystagmus [73–75]. Recent studies have shown the efficacy of the aminopyridines in the treatment of cerebellar nystagmus [75–79]. NMDA receptor antagonists such as memantine and alpha-2-delta calcium channel blocker such as gabapentin have been useful to treat the pendular nystagmus due to olivo-cerebellar dysfunction in the syndrome of ocular palatal tremor and that due of demyelinating disorders [80]. Contemporary studies have identified the role of ion channels in the pathogenesis of nystagmus and saccadic oscillations [80–82]. Therefore, it is critical to consider selective ion channel blockers as therapeutic options for the treatment of cerebellar nystagmus [81, 83].

Finally, the successful "ocular motor approach" can be applied to other types of disordered movement as tremor and cervical dystonia. For example, the concept of neural integration for holding the eyes still can be applied to the complex head movement patterns in a cervical dystonia, and to holding other parts of the body still also [84, 85]. In the ocular motor system, the abnormal function of the neural integrator leads to centripetal drifts of the eyes with consequent gaze-evoked nystagmus. Similar dysfunction of a head movement neural integrator leads to jerky head oscillations typical of cervical dystonia. Malfunction of a head neural integrator, due to impaired cerebellar, basal ganglia, or peripheral feedback [85], is analogous to ideas about abnormal feedback and the ocular motor integrator. The neural circuits controlling saccades and those controlling ballistic limb movements show many analogies. An example is applying the ideas underlying neuromimetic, ion channel-based models of saccadic oscillations to the hand oscillations (e.g., essential tremor) [81]. Such conductance-based models also suggest a physiological rationale for drugs used to treat essential tremor.

In summary, there are many reasons to study eye movements (Table 1). Eye movements are a common interface among scientific investigations by physicians, psychologists, biologists, biomedical engineers, rehabilitation specialists, and pharmacologists. Eye movements have been used to investigate function in humans, non-human primates, canines, rodents, and fish. They are easy to measure, quantify, and analyze; easy to manipulate in sophisticated behavioral paradigms; and can be subject to different types of transcranial stimulation. Finally, the study of eye movements is at the forefront of translational research. Eye movement studies in patients have led to fundamental discoveries of how the brain works, and conversely, the results of basic studies of the physiology of eye movements can be applied directly to the bedside for better treatment and diagnosis. It is not an exaggeration to say that the future is bright for all those interested in using eye movements to study how the brain works and how to better diagnose and treat our patients.

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Conflict of Interest The authors declare that they have no conflict of interest.

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