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What the Future Holds for the Study of Saccades

DAVID S. ZEE*

Department of Neurology, The Johns Hopkins University, School of Medicine, Baltimore, USA

Here we review the state of the art using saccadic eye movements as windows to the function of the normal brain and of the abnormal brain plagued by disease or trauma. By combining sophisticated behavioral paradigms with rigorous mathematical analysis and the latest imaging techniques one can use saccades as biomarkers of the highest level decision making to the lowest level basic machinery that generates premotor saccade commands. As technology advances saccades will become even more useful as immediate monitors of the state of the brain in disease and trauma and as a way to evaluate therapies.

K e y w o r d s: saccades, eye movements, superior colliculus, frontal eye fields

1. Introduction

Saccades are a fundamental motor behavior vital for survival for any animal that sees. We are above all visual creatures and saccades are widely represented in every part of the brain [1]. Early in evolution saccades served the needs of lateral-eyed afoveate animals with panoramic vision so they could be ready to respond to what might be coming into view as they moved through the environment. As animals became frontal-eyed and foveate, and especially in primates, saccades have become a more complex motor behavior that both reflects and serves the needs of higher cognitive processes including memory, attention and neglect, reward, choice, prediction and learning and adaptation. We understand well the functions of saccades and know much of their physiological and anatomical underpinnings [2, 3]. Functional and anatomical imaging studies and measurements of the electrical activity of the brain have revealed the widespread but interconnected nature of the neural networks that participate in

* Correspondence to: David S. Zee, Department of Neurology, Ophthalmology, Otolaryngology--Head and Neck Surgery, Neuroscience, Path 2-210, The Johns Hopkins Hospital, 600 N. Wolfe Street Baltimore, MD 21287, USA, e-mail: dzee@jhu.edu
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the generation of saccades [4–6]. Saccades are easy to elicit, easy to measure and easy to quantify. Technology has made it possible to record eye movements at the "bedside", even in ill patients in intensive care units, and so learn both the immediate effects of disease and trauma as well as the early compensatory mechanisms and strategies that the brain invokes in its attempt to assure survival.

As we develop new treatments we need easy to obtain and easy to quantify biomarkers that provide objective means of assaying brain function. Saccades are ideal for this task, and provide the necessary correlations among the anatomical, physiological and biochemical changes that occur with disease and its response to treatment. Saccades are also amenable to the rigor of mathematical and computational approaches, which has made them a model paradigm, for example, to understand how the brain learns to optimize its motor performance in the face of disease and trauma as well as with natural development and aging [7–13]. Saccades can also be used to probe higher level cognitive contributions to adaptation, for example, using saccades as an index to adaptation of the vestibulo-ocular reflex. The vestibulo-ocular reflex can be adapted in paradigms when, during sustained head rotation, a subject simply imagines a target in a new location or just pays attention to a target in a new location without actually looking at it [14]!

2. A Physiological and Control Systems Approach

The two pillars upon which much recent research about saccades has been based emerged about four decades ago. First there was the physiological and control systems approach. A key advance was the ability to record eye movements simultaneously with activity from single neurons within the brainstem of alert behaving monkeys. This activity could be related to the kinematic and dynamic characteristics of eye movements around all three axes of rotation: horizontal, vertical and torsion. These physiological findings were interpreted using control systems models of the flow of information within the neural circuits that produce the premotor commands for saccades. It followed naturally that one could interpret disorders of eye movements using the mathematical models of the bioengineer. On a personal note, I reached my epiphany for a career in eye movement research when David A. Robinson give a lecture to my class of neurology residents in which he used a control systems approach to dissect the abnormalities in internuclear ophthalmoplegia (a supranuclear deficit of adduction of one eye due to a lesion in the medial longitudinal fasciculus (MLF) that contains the axons of abducens interneurons that project to the oculomotor neurons that innervate the medial rectus muscle) [15]. He was able to pinpoint the lesion using a control systems diagram in which the flow of information from the premotor neurons generating eye position and eye velocity commands to the eye muscles was interrupted by the lesion in the MLF. Conversely, quantification of abnormal eye movements in patients, who unfortunately become experiments of nature caused by

disease and trauma, could be used to test concepts of how eye movement commands are generated in intact humans [3]. These clinical studies led to refinements and sometimes refutation of long held ideas about normal ocular motor control.

2.1. Slow Saccades and Internal Feedback Control

The study of patients who make slow saccades, from which the local feedback loop idea of saccade generation developed, typifies the iterative dance between basic science and clinical observation [16]. Initially saccades were conceived as ballistic, preprogrammed and once launched unable to be modified. An obligatory refractory period was thought to follow each saccade during which time a new saccade could not be produced. The slow saccades made by patients, however, could be interrupted and even turned around in midflight, behavior that the ballistic model could not explain. In place of the ballistic model a continuous control model of saccade generation emerged based on internal monitoring of the command to the eye in order to estimate where in the orbit the eye actually was as the saccade unfolded. This 'efference copy' of eye position was continuously compared with the internal estimate of the desired final position of the eye in the orbit to which the saccade must reach in order to deliver the fovea to its new target. In this construct the saccade was terminated automatically when the eye reached its goal, i.e., when the desired eye position and the internal efference copy of eye position became the same.

It was natural to apply this new model based on the slow saccades made by our patient to the control of saccades in normal individuals with the caveat, of course. The disease itself could have altered information processing for the control of saccades in a fundamental way that deviated from how movements are controlled by the normal brain. Nevertheless, physiological findings based on neural recordings of the activity of premotor saccade related 'burst' neurons within the brain stem fit well with this new model of internal feedback control of saccades [15]. Furthermore pathological studies of the brain of a patient who had made slow saccades in life confirmed that the burst neurons within the pons had succumbed to the degenerative process [17]. For almost four decades, with only a few, relatively small refinements, this local feedback model of saccade control has been the hypothetical construct that has driven most of the research into how the brainstem generates immediate premotor saccade commands.

2.2. Saccadic Oscillations

The local feedback model was also applied to understanding the origin of interrupted and unintended saccades in patients [3, 18]. For example, consider abnormal saccadic oscillations such as opsoclonus and ocular flutter in which the patient makes unwanted back to back saccades. Two features of the local feedback model make it susceptible to oscillations; the inherent delay in the local feedback loop, and the extremely high

frequency discharge of premotor saccade burst neuron, which is needed to drive the eyes at high speed. if the delay should become excessive there was a propensity for the system to become unstable and unwanted saccadic oscillations to emerge. The discovery of pause neurons within the pons, which project to and inhibit saccade burst neurons during steady fixation, was incorporated into the local feedback model to develop a hypothesis for saccade oscillations. Pause cells discharge steadily during fixation (and prevent any extraneous discharge of burst neurons) and perforce, must cease discharging when a saccade is to be made. In this way, saccadic oscillations could appear with a disturbance in which 1) pause cells no longer inhibited burst neurons during attempted fixation and 2) there was an increase in the delay in the internal feedback loop of eye position that is used to determine when the saccade is over. While this model provided a first approximation for understanding pathological saccadic oscillations it demanded physiologically implausible, large and variable increases in feedback loop delays to account for the different amplitudes and frequencies of saccadic oscillations shown by different patients or sometimes within the same patient. Furthermore normal individuals show saccadic oscillations under various circumstances including saccades combined with vergence movements, along the orthogonal axis when purely vertical large saccades are made and in so-called "voluntary nystagmus", which actually is a series of small-amplitude, back to back saccades one upon the other that many normal individuals can generate [19].

2.3. Neuromimetic Models of Saccade Generation

A conceptual breakthrough was developing models of the generation of saccades that embraced two new ideas. First was the discovery of local feedback loops between excitatory and inhibitory burst neurons within the brainstem with relatively brief delays between them. These delay loops were incorporated into the model and lent the saccadic system susceptible to oscillations in a more physiological way than by simply increasing the delay in the (longer) local feedback loop carrying the efference copy of eye position [20]. Secondly the role of membrane kinetics was incorporated into what was called a neuromimetic model for the generation of saccades [21]. The behavior of specific ion channels and receptor neurotransmitters became a core feature of the physiology of saccade behavior. The phenomenon of post-inhibitory rebound (PIR), in which a neuron shows a spontaneous, brief burst of activity when it is suddenly released from inhibition, played a key role in this new model of saccade generation. Variations of this model have been successfully used to explain slow saccades after experimental lesions in the pause cell region in monkeys [21], slow saccades made under closed eye lids by normal human subjects [22], saccadic oscillations made by normal human subjects during combined vergence and saccades [23], and pathological oscillations such as microsaccadic flutter in patients with familial saccadic oscillations [19, 24]. The importance of this approach for the clinician is that when oscillations are pathological or when uncalled for saccades occur, specific channels neural transmitter

activity can be targeted pharmacologically to reduce the excitability of the membrane and hence the propensity for intrusive extraneous saccades or saccadic oscillations [19, 25]. One's genetic background now becomes an important consideration in understanding why some patients show pathological saccadic oscillations and others don't when faced, for example, with the same metabolic insult. The degree to which one will be susceptible to saccadic oscillations will depend on one's inherent complement of receptor subtypes, and their relative ability to increase membrane excitability. As an example, the strength of PIR that one develops, and consequently, the amplitude of the acceleration of the eye at saccade onset and ultimately the propensity for oscillations, could depend upon the genetically determined, relative proportion of fast and slow-acting ion channel subtypes [19].

3. Saccades and Cognition

Around the same time that the physiological basis of saccades began to be understood, investigators realized that saccades could be used to probe higher level aspects of cognitive behavior. The standard 'reflexive' saccade paradigm, in which the subject was simply asked to look at a target that suddenly appeared in the visual periphery, was refined. New paradigms were devised to probe different aspects of voluntary motor behavior and included 'antisaccades' (look oppositely to the mirror location of a visual target) [26], memory-guided saccades (extinguish the peripheral target but do not look at its remembered location until cued to do so [27, 28], predictive saccades (follow a target that is jumping back and forth in a periodic fashion) and the gap-overlap paradigm (altering the relative timing of the disappearance of the fixation target and the appearance of the new target in the visual periphery) [29]. Again, as with control systems models, the study of human patients and monkeys provided information about the routes and patterns of processing of neural activity that mediated these behaviors. Early on this approach was applied to patients with frontal lobe lesions, who failed on the antisaccade task [30] and to patients with Parkinson's disease, who had particular difficulty generating volitional saccades between stationary targets [31]. Patients with Huntington's disease failed in antisaccade and predictive saccade paradigms [32] but, using the gap-overlap paradigm they were able to shift attention normally [33]. This pattern of abnormality suggested dysfunction in the frontal but not the parietal lobes. These studies using saccades showed that one can often pinpoint the areas of the brain that are affected by a disease process which in turn implies what their normal functions might be. Physiological studies in monkeys trained to make memory-guided saccades also revealed the importance of specific brain structures in the control of saccades [27]. Monkeys with chemically-induced transient focal lesions in the frontal lobes or basal ganglia had particular difficulty producing memory-guided saccades, providing clues to which structures within the brain play important roles in this type of behavior [27, 34, 35].

Using saccades to understand how the brain elaborates even more complex aspects of human behavior is a prominent feature of contemporary cognitive neuroscience. Both in normal individuals and in patients with neurological disorders, investigators have devised increasingly sophisticated paradigms that challenge and probe the mechanisms by which the brain accomplishes these high level tasks and how they are modified by brain lesions. In the first six months of 2011 alone searching Pub Med for the word 'saccade' elicits more than 600 citations with the majority dealing with some aspect of cognition. Areas of interest include studies on prediction and anticipation [36], and the ability to recognize change and adjust behavior accordingly [37]. Saccades are also used to study modulation of motor performance by what reward it might bring. The salience of individual parts in a complex visual environmental, which we scan with an attentional searchlight, determines how we pick and choose, and saccades are convenient indicators of these processes.

In monkeys, saccades are often used as nonverbal markers of various decision and attention processes. Indeed some of the most exciting discoveries about how different structures contribute to different aspects of cognition are made by recording neural activity within different structures during various behaviors and using saccades as a readout of what the monkey is "thinking". A recent example is the parsing of the contribution of the prefrontal cortex and striatum to the learning of novel abstract categories in which case the prefrontal cortex seems to be predominant with the striatum being more important for relatively simple stimulus-response associations [38].

3.1. Decision Making Reflected in Saccade Latency Distributions

Carpenter and colleagues analyzed the distributions of the latencies of saccades to a visual target suddenly presented in the periphery and developed the LATER (Linear Approach to Threshold with Ergodic Rate) model of neural decision making [39]. This model has been applied successfully to motor behaviors of various types and in various circumstances as well as to the evaluation of patients with neurological disorders. Schall and his colleagues followed on this approach looking for the neural correlates of decision making processes by recording from activity of neurons in the frontal lobes of monkeys using saccades as an index of decision making [40]. They developed a gated accumulator model of the "visual-motor cascade" that underlies transformation from stimulus to action [41]. Similarly, Watanabe et al., stimulating the caudate nucleus before pro- and anti-saccades, used the LATER model to understand the influence of the caudate nucleus on decision making [42].

The LATER model has been recently extended to account for the 'attentional' effects observed in gap-overlap paradigms [43]. Even the latencies of *incorrect responses* in a difficult paradigm requiring saccades to one color target but not to another, follow the same rules and provide insight into what leads to a *wrong* decision [44]. Similarly, when the cerebral cortex is heavily engaged otherwise in a complicated no-go task there are changes in the distribution of saccade latencies,

with an increased percentage of low latency, 'express saccades' and an increase in errors. From these results one can infer how the cerebral cortex influences lower structures within the brain stem such as the superior colliculus that generates the premotor commands for saccades [45].

3.2. Saccade Dynamics and Cognition

While we know that saccade latencies can reflect one's level of attention and interest in the task at hand, recent studies have also focused on cognitive influences on the dynamic properties of saccades such as their speed. We found that peak saccade velocity increased as the object of 'interest' changed from a nondescript visual target (meaningless noise) to a human face [46]. Shadmehr et al. have discussed the relationship of saccade dynamics (peak velocity) to the time one must wait until a reward becomes available ('temporal discounting'), again illustrating how saccades can be used to assay the complicated yet very human aspects of cognitive decision making [47].

3.3. Saccades, Imaging, Transcranial Magnetic Stimulation (TMS) and Cognition

As imaging technology advances, saccades will be used to dissect ever more subtle aspects of cognitive behavior. In normal individuals, combining eye movement behavior with diffusion MRI based tractography has revealed the cortical nodes associated with activity related to saccades and their anatomical interconnectivity [6]. Anatomical right-left hemispheral asymmetries were noted compatible with the hemispheral specialization in directing attention. Antisaccade performance in the elderly is a good predictor of performance on more traditional neuropsychological measures of executive function as well as grey matter volume in several key areas associated with inhibitory control; the left inferior frontal and right supplementary motor areas [48]. In patients with Parkinson's disease eye movement behavior, measures of executive function and gray matter volumes are correlated [49]. In patients with pre-manifest and manifest Huntington's disease, the latency for *vertical* antisaccades correlated best with atrophy in the left inferior parietal lobule, left superior frontal gyrus and both caudate nuclei [50]. Likewise, using fMRI and measuring the antisaccade error rate, these investigators showed that the activity in a reward detection network including the pre-supplementary motor area and dorsal anterior cingulate gyrus could be related to saccade performance in normals but not in HD patients. Magnetoelectroencephalography (MEG), an imaging technique with high temporal resolution, has been used to follow the activity within the brain as different types of saccades are generated as well how information about errors is processed [51]. Transcranial magnetic stimulation (TMS), another high temporal resolution technique, can be used to interrupt saccades at different time points during their generation and so reveal the flow of information through the brain from the inception of the decision whether or not to make a saccade to the completion of

the saccade itself. In this way the influence of different parts of the brain on saccade performance in various tasks including reading can be pinpointed [52–54].

4. Saccades as Biomarkers

Saccades have become quantitative biomarkers for neurological and psychiatric disorders, in both patients and 'unaffected' family members. In autism, unaffected first-degree relatives show a pattern of deficit in ocular motor control similar to those of affected patients including increased errors on the antisaccade task, saccade hypometria to visual targets and impaired generation of predictive saccades [55]. Patients with autism and Asperger's syndrome can be distinguished on the basis of their behavior on saccade tasks; the findings suggest differential involvement of the cerebellum in the two disorders [56]. Pre-symptomatic carriers of Huntington's disease can be identified using sophisticated saccade paradigms [50, 57]. Traumatic brain injury has been a diagnosis in search of quantitative behavioral markers and saccades too have helped meet this need [58]. Saccades and fMRI have been used to dissect out the relative contributions of the ipsilateral and contralateral hemispheres to patterns of recovery following strokes [59]. One can see that as technology advances, making recording of eye movements easier in extreme circumstances such as the intensive care unit, we will be able to take the rigor of mathematical models of decision making to the bedside to understand how the brain malfunctions when stressed acutely and how it recovers, both naturally and with our interventions. Recent examples include using saccades to quantify the effects of acute metabolic derangements and of treatments for stroke [60–62].

Finally, there has been considerable progress in relating performance on oculomotor motor tasks to the activity of specific neural transmitters such as dopamine [63], GABA [64–66] or acetylcholine [67], using physiological studies in monkeys as well as MRI spectroscopy and PET scanning in humans. By relating behavior to the levels and location of different neurotransmitters within the brain, we can design targeted interventions for disease as well as monitor how therapy alters the neurochemical milieu of the brain. One can extrapolate confidently from these few recent examples that the study of saccades will become a pillar for understanding the how the brain functions in its normal intact state and when it is under attack by disease or damaged by trauma.

5. Conclusion (see Table)

Clinicians of many ilks including neurologists, psychiatrists, ophthalmologists, otolaryngologists and physical therapists use saccades to assay the function of the brain, the ears, the eyes and the psyches of their patients. The study of eye move-

ments is also in the province of psychologists, bioengineers, basic neurophysiologists and pharmacologists; they all use saccades to assay brain functions, and it is not an exaggeration to claim that saccades are truly a window to the function of every corner of the brain. Saccades have been the behavior of choice in studies in nonhuman primates that relate the behavior of single neurons to higher level processing of sensory information, and more complex perceptual judgments and decision making. Conversely as we move down the evolutionary ladder to simpler animals such as zebra fish and mice we use saccades to relate behavior to the microcircuits of the brain, including anatomy, ion channel physiology and membrane kinetics. Saccades are also an ideal way to study genetic mutants and the effects of artificially manipulating different parts of the genome to determine how altered encoding of proteins is reflected in phenotypic expression of behavior, for example, in capabilities for motor learning. Finally and perhaps most importantly, knowledge of saccades is at the forefront of translational research. Studies in patients have led to fundamental discoveries of how the brain works, and conversely, results of basic studies of the physiology of saccades can be directly applied to the bedside for better treatment and diagnosis. The future is bright for those of us interested in using saccades to study how the brain works and how to better serve our patients with neurological and psychiatric disease.

TABLE: WHY STUDY SACCADES

- Widely represented in the brain since we are above all visual creatures and without saccades to bring images to the fovea we could not see well enough to survive.
- Functions well understood and divided into a recognizable hierarchy with specific physiological properties and anatomical substrates.
- Easy to elicit, measure and quantify.
- Amenable to the rigor of mathematical and computational approaches.
- Easily combined with other methods (e.g., fMRI, MEG, TMS) to pinpoint and follow the flow of information through the brain as different behaviors are elaborated.
- Clinicians (neurologists, psychiatrists, otolaryngologists, ophthalmologists) psychologists, bioengineers, basic neurophysiologists and pharmacologists, all use saccades to assay brain functions.
- Useful biomarkers in neurological and psychiatric disease, development and aging, personality traits and talents, rapidly fluctuating states of neurological function.
- Convenient for studying cognition including prediction, memory, reward and attribution of value, attention, decision making, impulsivity, learning and adaptation, boredom.
- For motor control scientists, saccades are especially attractive for study since eye muscles lack a stretch reflex and move their effector (the globe) around a single axis (one joint).
- Saccades are easily measured in experimental animal models from monkeys to mice to pigeons to frogs to goldfish to zebra fish.
- Relating the behavior of saccades to neurotransmitters, ion channel functions, membrane kinetics and neural circuitry is relatively easy.
- 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.

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