REVIEW

A TALE OF TWO SPECIES: NEURAL INTEGRATION IN ZEBRAFISH AND MONKEYS

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Abstract—Selection of a model organism creates tension between competing constraints. The recent explosion of modern molecular techniques has revolutionized the analysis of neural systems in organisms that are amenable to genetic techniques. Yet, the non-human primate remains the gold-standard for the analysis of the neural basis of behavior, and as a bridge to the operation of the human brain. The challenge is to generalize across species in a way that exposes the operation of circuits as well as the relationship of circuits to behavior. Eye movements provide an opportunity to cross the bridge from mechanism to behavior through research on diverse species. Here, we review experiments and computational studies on a circuit function called ''neural integration'' that occurs in the brainstems of larval zebrafish, primates, and species ''in between''. We show that analysis of circuit structure using modern molecular and imaging approaches in zebrafish has remarkable explanatory power for details of the responses of integrator neurons in the monkey. The combination of research from the two species has led to a much stronger hypothesis for the implementation of the neural integrator than could have been achieved using either species alone.

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Abbreviations: FEF, frontal eye field; FTNs, floccular target neurons.

EYE MOVEMENTS AS A MODEL SYSTEM

The eye movement system is one of the most-studied and best-understood sensory-motor systems in neuroscience. We move our eyes for two clearly-defined purposes: to shift the eyes to point them at objects of interest, and to rotate the eyes smoothly so that they remain pointed at objects of interest in face of self-motion or object-motion. Eye movement is a particularly apt movement to understand because of its power as a diagnostic tool for neurological and neuropsychiatric disorders (Klin et al., 2002; Garbutt et al., 2008; Jones et al., 2008). Research on monkeys should provide the ''final common path'' to understanding human eye movements in health and disease. Yet, the machinery of the eyes and the behaviors have been preserved during evolution so that many animal models can be used to understand the neural circuit basis for eye movements.

Research on humans and non-human primates has made steps in understanding eye motor control that are essential for research on any motor system. First, analysis of the motor behavior has dissected eye movement into its components and categorized different types of movements. We make rapid, saccadic eye movements to reorient the gaze. We use the vestibulo-ocular reflex to stabilize gaze in the face of our own motion. We use smooth pursuit eye movements to keep the fovea pointed at moving objects. Second, recordings of the electrical activity of neurons in the brainstem have revealed details of the final motor command signals. As a consequence, it is easier to interpret the responses of other neurons in relation to the signals that appear on motoneurons (Fuchs and Luschei, 1970; Robinson, 1970; Robinson and Keller, 1972). Recordings that work backward from the motor nuclei have revealed the discharge properties of neurons in premotor brainstem nuclei, and have suggested how the premotor circuits might be organized (Robinson, 1981; Sparks, 2002). Third, the relative simplicity of the eye movement system has made it tractable for computational modeling,

which provides the language needed to understand any neural system.

Monkeys have provided an excellent animal model for understanding many aspects of how the brain controls eye movements. Causal manipulations, such as inactivation or stimulation of specific groups of neurons, have identified the brain areas that control different kinds of eye movements (Robinson, 1972; Wurtz and Goldberg, 1972a; Schiller et al., 1980; Rambold et al., 2002). Because of the excellent understanding of the final motor pathways and behavior, eye movement has provided an excellent model system for studying higher commands for movement in areas such as superior colliculus (Wurtz and Goldberg, 1972b; Zenon and Krauzlis, 2012), basal ganglia (Hikosaka and Wurtz, 1983; Lau and Glimcher, 2008), cerebellum (Lisberger and Fuchs, 1974; Shidara et al., 1993), and frontal cortex (Bruce and Goldberg, 1985; Gottlieb et al., 1994). Eye movements also have provided the substrate for advancing knowledge about the neural mechanisms of perceptual decisions (Platt and Glimcher, 1999; Shadlen and Newsome, 2001). Overall, there is a remarkable body of work that describes neural activity during oculomotor behavior in monkeys. Nothing comparable to it exists in any other species.

Monkey research has been challenged to link function to structure, but there have been some notable successes. These have been based mainly on using electrical stimulation in the brain to identify neurons according to their connections to other neurons, or at least according to their anatomical projections. For example, identification of the neurons in the brainstem that receive monosynaptic inhibition from the floccular complex of the cerebellum has revealed their role in driving smooth eye movements (Lisberger et al., 1994b; Zhang et al., 1995; Ramachandran and Lisberger, 2008; Joshua et al., 2013) and motor learning (Lisberger and Pavelko, 1988; Lisberger et al., 1994a). Antidromic activation has revealed rules for distributing output from the cortex by studying the functional discharge properties during eye movements of the neurons that project from the frontal eye field (FEF) to the reticular formation, the pons and the superior colliculus (Segraves and Goldberg, 1987; Segraves, 1992; Ono and Mustari, 2009). Electrical stimulation has outlined a pathway that transmits an efference copy of the command for saccadic eye movements from the superior colliculus through the thalamus to the FEF (Sommer and Wurtz, 2002).

The explosion of new techniques for studying neural networks has created opportunities for a new kind of analysis of neural circuits and how they work. It now is possible to go beyond the traditional approaches used in monkey research, and to answer questions that were intractable in the past. For example, imaging of calcium signals makes it possible to record from many nearby neurons simultaneously with a temporal resolution that is good enough to capture the relationships between neural and behavioral or stimulus dynamics (Stosiek et al., 2003; Rothschild et al., 2010; Miri et al., 2011). Activation of specific subpopulations of neurons through optogenetics provides a carefully controlled tool for

dissection of neural circuits in behaving animals (Han and Boyden, 2007). Genetic manipulations make it possible to eliminate, reversibly inactivate, or activate specific types of neurons (Schonewille et al., 2011). These modern approaches have enormous potential for understanding how neural circuits work, but they are challenging to apply in non-human primates.

Because of the differences in techniques that can be applied efficiently in different species, analysis of the primate oculomotor system faces a challenge. Primates offer the most impressive, flexible, and repeatable oculomotor behavior along with the ability to study eye movements and the associated neural activity on a millisecond time scale. Yet, advances are stymied because of the challenges of measuring the architecture and electrical activity within defined circuits in monkeys. The measurements needed in monkeys are possible using modern imaging and molecular tools in non-primate model organisms, but these organisms lack the exquisite-control of motor behaviors seen in primates.

We see two ways to bridge the gap between species. One is to apply modern molecular and viral techniques in monkeys, an approach taken by a couple of laboratories (Jazayeri et al., 2012; Adelsberger et al., 2014). The other way is to study the same behavioral phenomena in multiple species, leveraging the advantages of each. The key is to use experimental design and data analyses that are similar enough across species to allow the unified understanding to be greater than the sum of its parts. We have adopted this second approach to understand the implementation of "neural integration" in the oculomotor brainstem. Neural integration is a computation that is common to primates, rodents and fish. While expressed in its purest form in the oculomotor system for converting transient commands for eye movement into sustained signals, neural integration also is important to retain a working memory of a transient event (Goldman-Rakic, 1995), and to accumulate evidence in favor of particular perceptual decisions (Shadlen and Newsome, 2001; Brunton et al., 2013).

THE OCULOMOTOR NEURAL INTEGRATOR

The need for a neural integrator in the oculomotor system (Fig. 1A) arises from the discharge properties of extraocular motoneurons. The output of the oculomotor system is understood very well through measures of the forces generated by the extraocular muscles (Robinson, 1964; Miller et al., 2002; Davis-Lopez de Carrizosa et al., 2011) and recordings from motoneurons that control eye muscles (Fuchs and Luschei, 1970; Keller and Robinson, 1972; Sylvestre and Cullen, 1999). During rapid, saccadic eye movements, motoneurons emit a transient burst of action potentials followed by a change in steady firing rate related to eye position (Fig. 1B, blue line). Muscle force shows a pulse during movement that is followed by sustained force at the end of the eye movement. The appearance of sustained force in the muscles was the first hint of a neural integrator that holds the eye steady at eccentric positions. Integration would explain the fact that motoneurons have sustained activity