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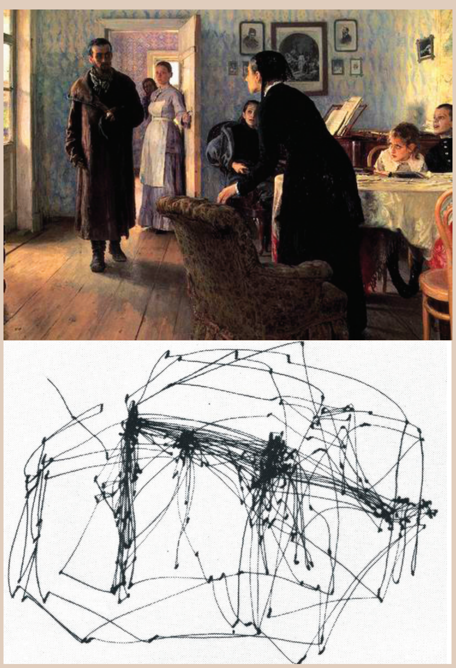
Point of View

THE EYE RESEARCH INSTITUTE UNIVERSITY OF WISCONSIN–MADISON

Ready, See, Go!

A scene in the movie "Awakenings," based on the book by Oliver Sacks, shows a woman who shuffles as she walks to a water fountain. With this slow, hesitant gait characteristic of parkinsonism, she progresses steadily over the high contrast, black-and-white tile floor. But she halts abruptly, unable to proceed, when the floor surface changes to solid gray. The presence of visual stimuli (for her, the high contrast flooring) can often help patients with Parkinson's disease overcome their movement disability; but absent visual contrast (the solid gray floor), their internal ability to generate movement is inoperable.



Alfred Yarbus' seminal study in 1967 illustrated that eye movement patterns correspond to the underlying structure in an image. In one test, subjects were asked to determine the ages of the people in the painting "An Unexpected Visitor," by I.E. Repin, while their eye movements were tracked. The lines in the image under the painting represent the saccades – eye sweeps – made by the viewer, and the dots were the points where gaze rested. The most intense areas of line tracings clearly overlap the faces and bodies of the people depicted in the images, showing that the eye movement patterns clearly correspond to the task given to the subject.

In health and disease alike, how does what we see translate into what we do? Scanning a broad visual field, our eyes constantly feed information to our brains; but how do we choose where to direct our attention? Behavioral neurophysiologist Michele A. Basso, PhD, associate professor of physiology and member of the UW Eye Research Institute, is intrigued by such questions. To understand processes related to choice and decision-making, Basso studies how the brain takes visual information and transforms it into specific eye movements.

Graduate student Byounghoon Kim and Michele Basso, PhD, look at the eye movement behavior of a non-human primate in a decision-making task.

Tracking saccades, rapid eye movements from one position to another, is key to learning about the neural mechanisms linking vision and action. The sudden appearance of a bright light initiates a saccade that draws our eyes reflexively toward that target; or, we may volitionally direct our gaze to a remembered point. By manipulating visual tasks that induce different types of saccades, Basso can focus on cognitive processes such as target selection, memory and learning.

"Each task has different demands, allowing for the assessment of the integrity of brain pathways in health and disease," explains Basso. "In a saccade task that requires memory, for example, an illuminated point appears in the center of a screen and the subject maintains gaze on its location. A second point briefly appears at another screen location, while the subject is instructed to retain eye focus on the first point. After a short delay, the first point disappears, signaling the subject to make a saccade to the location of the second flashed target point. This task provides a test of spatial working memory." During this simple task, Basso takes electrophysiological recordings of neuron activity in non-human primates, monitoring responses in brain locations such as the superior colliculus and the basal ganglia, brain areas involved in transforming visual signals into internal representations that ultimately become commands to move the eyes.

What is it that allows patients with Parkinson's disease to move in response to visual cues but prevents movement in the absence of visual stimulus to guide them? To unravel this paradox, Basso uses her study of healthy animal subjects as a baseline to advance knowledge of neural processing behind basic eye movement behaviors in conjunction with clinicians Karl Sillay, MD, UW Neurological Surgery and Ming Cheng, MD, Brown University Neurosurgery Foundation. Together they investigate how the transformation of visual information to movement goes awry in humans with neurological diseases.

In one study, for example, patients are asked to choose a single visual stimulus from among four possible visual stimuli. Their choice depends upon a cue that appears in the center of a screen. In some cases the cue is very clear—an arrow may direct them to look to the spot on the right. In other cases the cue is subtle and patients must rely on memory of their past choices to aid in determining the current correct choice. Clinical studies of eye movements in the context of this sensory uncertainty may lead to therapies for Parkinson's disease and could enhance the ability of patients to make these eye movement choices.

The brain areas involved in Parkinson's disease and Huntington's disease also appear to be involved in other neuropsychiatric diseases such as schizophrenia, obsessive-compulsive disorder, Tourette's syndrome, and autism. "All of the patients diagnosed with these diseases have the common denominator of eye movement disorders because of disruption to the loop of information conveyed between the cortex and basal ganglia," observes Basso. "Studying eye movement choices and saccadic eye movements may bring insights into the fundamental mechanisms of these diseases and can provide a window into the brain of affected individuals," Basso notes. This non-invasive means of investigating movement associated with mental processes and their supporting neural circuits can help investigators draw conclusions and propose models about the brain circuitry problems behind these disorders.

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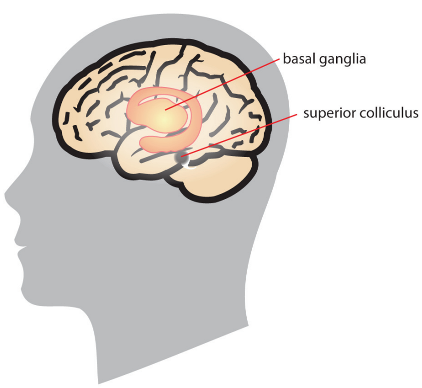
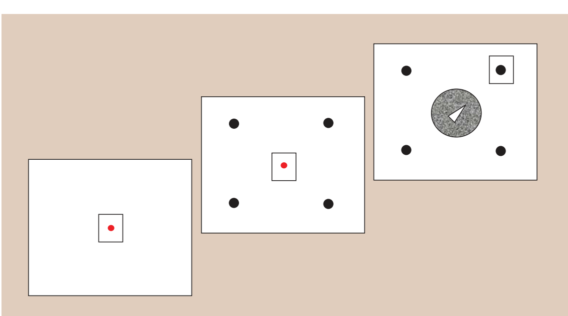


The superior colliculus and the basal ganglia are brain areas involved in converting visual signals into eye movements.

By designing tasks whereby patients have to exhibit their internal decisions via eye movements, it may be possible to detect subtleties in disease symptoms that can facilitate earlier diagnosis. "Sixty to eighty percent of brain cell loss occurs before disease symptoms are evident. Future development of an eye movement test may have valuable clinical application," posits Basso, "enabling us to discern degenerative disease evidence sooner, well prior to overt symptoms; earlier diagnosis and intervention may ultimately delay or even prevent further degeneration."



This set of panels shows steps in which a subject receives clear sensory information guiding choice of eye movement. After first looking at the center red spot, four other spots appear. Then a central cue appears with an arrow that is either easy (as depicted) or difficult to see. The task is to make a saccade to the spot that corresponds to the direction of the arrow.

Basso also brings knowledge gained from studying eye movements and neural activity to bear at a cellular level. Using rodent models, she and collaborators Meyer Jackson, PhD, UW professor of physiology, and graduate student Corinne Vokoun can explore *in vitro* the properties of the same brain circuits as in healthy non-human primates and in humans with neurological disorders. They are looking at how brain cells form the circuits that guide eye movements and cognition. This arm of Basso's research closes the loop from cells and circuits to mind, behavior and disease.

Each aspect of Basso's studies is grounded in her strong commitment to basic science approaches. Animated by enthusiasm, Basso shares her philosophy: "Curiosity-driven basic science appears to yield only piecemeal steps forward. These small steps, however, have advanced our knowledge immeasurably. Although we need to be cognizant of the grand horizon and ultimate clinical goals, we must also understand how science works incrementally." Step by step, Basso—with her students, subjects and collaborators—is tracking along a zigzag discovery path toward understanding debilitating neurological disorders.

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