always to give rigorous quantitative expression to qualitative concepts. This was encapsulated in his famous review in 1948 of the properties of haem proteins. A notable paper by Wyman and D.W. Allen in 1951 could be said to prefigure what later became known as the allosteric hypothesis. After his return to (more or less) full-time science Wyman developed the theoretical basis of the scheme of Monod and Jacob, which postulated an equilibrium between two conformational states, one of high, the other of lower oxygen (or more generally ligand) affinity; this became the MWC model for ligand-controlled activity of subunit proteins. The theory of linked functions ('A Second Look') occupied another widely cited review in 1964.

Later papers enlarged on the thermodynamics of ligand interactions and linked functions. On occasion a certain self-indulgence, which would be harder to sustain today, revealed itself. A paper in the *Journal of Molecular Biology* in 1965, in which Wyman outlined his concept of binding potentials, began: 'In the course of reading over the other day, at a window by the sea, the page proof of an article on linkage I was suddenly struck …' The extent to which protein chemists have found uses for the binding potential and some of the other later elaborations of the theory of linked functions is uncertain. There remain Wyman's two books, the first with John Edsall, relevant and enlightening to this day, and the second, published 32 years later, with S.J. Gill on *Binding and Linkage*, also still widely used.

One is left at the end of the story with the impression that the solitary thread which ran unbroken through Wyman's peculiar and varied life was an intense scientific curiosity. In 1902 the Oxford physicist, Nevil Story Maskelyne, nearing the end of his life, was forced to submit to an operation, from which he was not expected to recover (although in the event he did). His last words before the anaesthetic took effect were: 'I must live: I want to know more about radium'. Wyman did better than Maskelyne, for he had the satisfaction of seeing his equations made manifest in the beautiful structures that Max Perutz brought to light.

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Quick guide

Saccadic suppression

Bart Krekelberg

How do we see? Seeing necessarily involves moving our eyes. Even though we are usually unaware of it, we move our eyes about twice every second. These eye movements are highly targeted. For instance, when asked to judge the wealth of people in a picture, our eye movements target their clothes; when asked about their age, we look at their faces. As a consequence of these eye movements, the input to the visual system is much like an amateur video; short, relatively stable snapshots, alternated with rapid, jerky movements. Research into visual stability aims to explain how the brain transforms this confusing input into the stable perceptual experience of our everyday lives.

Why do we make so many eye movements? The human eye has about 100 million photoreceptors. Unlike the pixels on a 100 megapixel camera, however, these photoreceptors are not distributed evenly: near the center of the retina, their density increases tenfold. As a consequence, high resolution vision is only possible by pointing your eyes in the right direction. For instance, imagine driving a car with your gaze straight ahead and your hands on the steering wheel in the 10 and 2 o'clock positions. In this situation you are legally blind to everything that happens outside the narrow cone described by your arms. The fact that this statement contradicts your perceptual experience shows that eye movements are effortless, subconscious, and very effective in providing the illusion that you have high resolution vision everywhere.

An alternative design of the eye could have been a uniformly high density of photoreceptors, without the ability to move the eye. From an evolutionary perspective, it must have been advantageous to have a small, high-density region of photoreceptors, combined with the muscles and control mechanisms to move those photoreceptors around. Constantly moving the eyes, however, does create problems of how the visual input should be interpreted.

What are saccades and what is suppressed? Saccades are the rapid eye movements that bring objects of interest onto the central, highly sensitive part of the retina. During each saccade, the image of the world moves across the retina. Saccadic suppression refers to the behavioral observation that healthy humans under normal circumstances do not perceive this motion. A striking demonstration of this phenomenon can be experienced by looking in a mirror and making eye movements back and forth from left to right. You will see yourself staring back at you, but never observe your eyes in motion. This is not because the eyes move 'too fast to be seen'. Someone who looks over your shoulder can easily confirm this. This is also not because you are looking into the mirror at an angle while your eyes are moving back and forth; the fact that you can see your mouth while looking at your eyes demonstrates this.

Saccadic suppression is particularly strong for visual input that provides information on position or motion. For instance, if a visual object is moved to a new position during a saccade, this displacement is rarely noticed. Similarly, a pattern of black and white stripes that strongly stimulates the motion pathways of the brain and is easily visible when the eyes are stationary may go unnoticed when it is flashed during an eye movement. Interestingly, saccadic suppression begins just before (~75 ms) the eye starts to move, is strongest at the start of the eye movement, and rapidly weakens once the eye has landed in its new position.

What does 'suppression' really mean? Even though an observer may report not seeing a visual pattern flashed during an eye movement, that invisible stimulus can still affect what the observer sees after the eye movement. Hence, saccadic suppression removes the stimulus from awareness, but does not prevent the stimulus from being processed by the visual system.

Suppression is a reduced perceptual awareness, or reduced visibility. That saccadic suppression exists, is a behavioral fact; why, how, and where in the brain it happens is a matter of ongoing scientific debate.

How could suppression be achieved? There are several ways in which a visual input could become unnoticeable. The simplest to envision is probably a reduction of the visual response of the relevant neurons. If most neurons respond less, then it is likely that the observer will see less. Another possible mechanism relies on the fact that, once the eye has moved to its new position, a clear image will be on the retina. The neural activity corresponding to this new (and important) image could 'wipe out' the information that entered the visual system during the eye movement.

There are other possibilities: for instance, the eye movement could introduce so much noise in the visual system that it can no longer distinguish among different inputs. Or the eye movement could generate such strong neural activity that it saturates the visual system and new inputs would not lead to changes in the response. There is no agreement about which of these mechanisms is the correct one; possibly all of them play a role.

Where in the brain does suppression take place? Some have claimed that suppression begins in the retina because, during the rapid acceleration and deceleration of the saccade, the photoreceptors are bent and therefore collect less light. This explanation is almost certainly incorrect, if only because we know that suppression also affects visual input that is presented just before the eye starts to move.

In the brain, many neurons respond differently to visual input presented just before, or during an eye movement. Relating those changes in neural activity to the behavioral phenomenon of saccadic suppression, however, is far from trivial as it requires not just knowing how the neurons respond, but how the rest of the brain uses those neurons. Neurons in one visual area, MST, which is specialized for large-scale motion detection, for instance, generally reduce their activity around saccades. Interestingly, this reduction starts before the eye movement and follows a time course that matches the behavioral phenomenon. These neurons are good candidates for a mechanism of saccadic suppression that relies on response suppression. On the other hand, neurons in the visual thalamus as well as in some parietal areas mainly show an increased response during eye movements. This could reflect a saturation mechanism.

These are only two of the many examples of neural evidence that are consistent with one of the possible mechanisms. This embarrassment of solutions suggests that the question "where does suppression take place?" may be ill-posed. Instead, it may be more fruitful to think about the functional role that each area — or even each neuron — plays, and what that neuron would require to function appropriately in the presence of eye movements.

Do other sensory modalities have similar mechanisms? In very general terms, the issue that saccadic suppression tries to deal with is that sensory input generated by the actions of the observer should most often simply be ignored. A general solution for this is to use a signal from a motor control area to change processing in a sensory area. Such signals have been termed corollary discharge, or efference copy signals. A striking example in the auditory system can be seen in the cricket, which can produce 100 dB sound levels that could be deafening to its own ears if not for a corollary discharge mechanism that inhibits auditory neurons whenever the cricket starts singing.

How do cameras solve this problem? Moving a photo camera while taking a picture leads to blurry photographs. This is the same problem that saccadic suppression tries to solve. Many cameras determine whether exposure settings are such that camera movement is likely. Some prevent pictures from being taken when this is the case. Most cameras, however, provide a warning sign to the photographer, who decides whether a blurry picture is better than no picture. This could be seen as analogous to eye control areas in the brain sending corollary discharge to visual areas so that some areas may decide to ignore the subsequent input (take no picture), while others may process the input in a manner that is different from standard processing, but nevertheless extracts some useful information (take a blurry picture). More advanced cameras detect the real motion of the camera and move either the lens or the electronic element that captures the image in the opposite direction. As a consequence, the image is stable. The brain does not appear to use such an advanced mechanism during saccades.

Does everyone have saccadic suppression? There are reports of patients in the early stages of schizophrenia who state that "if I move, the picture in front of me changes". This suggests that their mechanism of saccadic suppression is impaired. Other, more cognitive aspects of schizophrenia may also involve impairments of a self-monitoring or corollary discharge mechanism. For instance, a reduced ability to distinguish self-generated thoughts from real auditory input could lead a patient to hear voices, or experience thought-control. One of the goals of studying corollary discharge in sensory systems such as vision and audition is to provide insight into the underlying mechanisms, and eventually use those insights to understand or even cure diseases in which these mechanisms are impaired.

Where can I find out more?

Bremmer, F., Kubischik, M., Hoffmann, K., and Krekelberg, B. (2009). **Neural dynamics** of saccadic suppression. J. Neurosci. *40*, 12374–12383.

Crapse, T.B., and Sommer M.A. (2008). Corollary discharge across the animal kingdom, Nat. Rev. Neurosci. *9*, 587–600.

Ibbotson, M.R., Cloherty, S.L. (2009). Saccadic omission: suppression or temporal masking? Curr. Biol. *19*, R493–R496.

Stephan, K. E., Friston, K.J., and Frith, C. D. (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schiz. Bull. *35*, 509–527.

Watson, T.L., and Krekelberg, B. (2009). The relationship between saccadic suppression and perceptual stability. Curr. Biol. *19*, 1040–1043.

Wurtz, R.H. (2008). Neuronal mechanisms of visual stability. Vis. Res. *48*, 2070–2089.

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