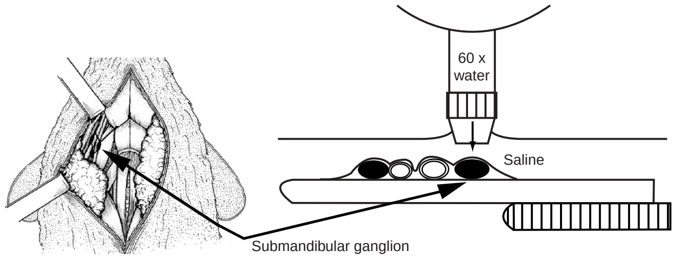

Figure 1 Diagram of experimental methods.

cles and pushed long-term *in vivo* imaging to a new level[2]. Using the rodent parasympathetic submandibular ganglion preparation that the Lichtman and Purves labs have been perfecting over the past decades[3,4], Gan *et al.*[2] now show that at least some synaptic connections become increasingly morphologically stable as the nervous system matures, changing hardly at all after middle age (in a mouse ~6–12 months). The reported observations were only possible by combining a number of cutting-edge technologies: microsurgical preparation, allowing the same area to be imaged several times during a period of more than a year, confocal microscopy and transgenic expression of green fluorescence protein (GFP), allowing stable fluorescent labeling of cells. Also, the submandibular ganglion preparation used by Gan *et al.*[2] may be particularly conducive to such studies as the neurons are either completely isolated or present in small clusters on the salivary ducts, making relocation and imaging easier.

This work follows on the heels of two studies[5,6] that examined neuronal morphology over time in the cerebral cortex and, incidentally, used very similar transgenic animals[7]. Interestingly, these earlier studies came to contradictory conclusions concerning the stability of dendritic spines. One found that in the mouse barrel cortex, although dendritic structure was stable over weeks, spines appeared and disappeared[5]. But according to the other study[6], which used similar GFP-expressing mice, spines on pyramidal neurons in layer 5 of primary visual cortex show remarkable plasticity during the critical period early in development, but become much more stable in the adult. The current study by Gan *et al.*[2] now adds complementary results on presynaptic morphological stability and thus provides further information about how stable the adult nervous system really is.

There are, however, a number of issues that still need to be resolved, including the physiological relevance of morphological stability or plasticity. Could a ganglionic synapse, which seems to serve as a relay, with reliable action potential initiation in the postsynaptic cell following every presynaptic spike, ever be the site of and hence model for 'memory'? Are morphological changes correlated to memory formation at all, as has been suggested, for example, by observations of spine genesis during synaptic stimulation[8,9]? Then there is, of course, the question of what the biochemical mechanisms are that provide stability and malleability, respectively, to synaptic morphology. The system used by Gan *et al.*[2] may be well suited to study this very question, as the effects of transgenic and pharmacological manipulations on long-term morphological stability can probability be assessed more clearly and quantitatively in the submandibular ganglion than, say, in cortex.

1. Golgi, C. Gazzetta Medica Italiana, Lombardia **33**, 244–246 (1873).
2. Gan, W.B., Kwon, E., Feng, G., Sanes, J.R. & Lichtman, J.W. *Nat. Neurosci.* **6**, 956–960 (2003).
3. Lichtman, J.W. *J. Physiol.* (*Lond.*) **273**, 155–177 (1977).
4. Purves, D. & Lichtman, J.W. *J. Neurosci.* **7**, 1492–1497 (1987).
5. Trachtenberg, J.T. *et al. Nature* **420**, 788–794 (2002).
6. Grutzendler, J., Kasthuri, N. & Gan, W.B. *Nature* **420**, 812–816 (2002).
7. Feng, G. *et al. Neuron* **28**, 41–51 (2000).
8. Engert, F. & Bonhoeffer, T. *Nature* **399**, 66–70 (1999).
9. Maletic-Savatic, M., Malinow, R. & Svoboda, K. *Science* **283**, 1923–1927 (1999).

© 2003 Nature Publishing Group http://www.nature.com/natureneuroscience

Seeing after blindness

Richard L Gregory

The unusual case of a man who regained his sight after 40 years of blindness allows researchers to examine the neural and behavioral effects of losing visual experience on the establishment and maintenance of visual system function in humans.

Sight given to an adult following blindness from infancy is interesting for what this unusual occurrence can tell us about the normal development of vision. But of course the adult is not a baby suspended in time, as he has lost the normal 'critical development' periods and is armed with knowledge of the world from years of exploratory touch and from sighted people through language. In this issue, a thorough characterization of such a subject shows that he had instant sight for identification of simple shapes like a circle or triangle, with interesting abnormalities and a need for learning about more complicated visual objects, and almost completely spared motion perception.

The author is Emeritus Professor of Neuropsychology, Department of Experimental Psychology, University of Bristol, 8 Woodland Road, Clifton, Bristol BS8 1TN, UK.
e-mail: richard.gregory@bristol.ac.uk

The case reported here by Fine *et al.*[1] is of a man (MM) who regained sight in his early forties, having lost one eye and the sight in his other eye in a chemical accident at three and a half years of age. The study was carried out by an expert team of visual scientists who used psychophysics, functional magnetic resonance imaging (fMRI) and electroretinograms to characterize MM's visual abilities, brain function and eye function. The case is also unusual in that the subject is an intelligent and remarkably successful person who was a champion blind skier. The results broadly confirm several reported cases over the last half-century, as well as add important new findings.

The empiricist philosopher John Locke[2] first addressed the issue of whether experience is important in the development of

© 2003 Nature Publishing Group http://www.nature.com/natureneuroscience

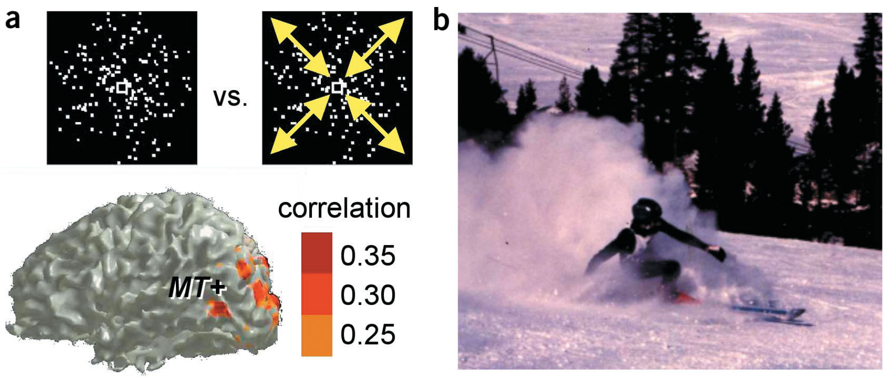

Figure 1 MM inside and outside. (**a**) MM's left-hemisphere activation in areas MT+ and occipital cortex in response to stationary versus moving dot stimuli. Regions responding at a correlation value above 0.25 are shown, and the color-coding represents the correlation value of each voxel. (**b**) MM on the slopes at Kirkwood, California.

vision in 1694. The question was originally raised in a letter from his Dublin lawyer friend William Molyneux:

"Suppose a man born blind, and now adult, and taught by his touch to distinguish between a cube and a sphere of the same metal . . . and the blind man made to see. Query, whether by his sight before he touched them, could he distinguish and tell which was the globe and which the cube? . . . The acute and judicious proposer answers: not. For though he has attained the experience that what affects his touch, yet he has not yet attained the experience of how the globe, how the cube, affects his touch so and so, must affect his sight, so and so…"

There were reported cases of recovery of sight long before Locke, by removal of the eyes' lenses made opaque with cataract, dating from 1020. These were collected by H. M. von Senden[3] in 1932. They misleadingly suggested—as the eyes took weeks or months to function optically, following an operation performed in primitive conditions—that any useful vision was very slow to develop. These cases led to the idea that all seeing is learned through visual experience. Only recently has it been realized that babies have considerable vision within hours of birth, even mirroring their mother's expressions. Considerable immediate sight is also found in long-blind adults with corneal transplants or artificial lenses giving instant retinal images, though these people have interesting impairments and abnormalities of vision.

Delaying the operation to restore vision until adulthood, advantageous though it may be for the experimenter, is more than inconvenient for the patient, and so must have some reason, usually a technical one. The reason in this new case of MM was a failed early attempt, with later success achieved with recently available stem cells. In the SB case[4] that Wallace and I reported in 1963 (www.richardgregory.org), the operation was delayed until the patient was 52 because of the poor state of his eyes and because the previously reported cases from von Senden had led the doctors to expect that the operation would fail to restore the patient's sight. However, once corneal banks were established around that time, the increased availability of corneas made the cost of this expected failure more acceptable.

Generally, the recent corneal transplant cases, and also cases in which artificial lenses give instant retinal images, do not show John Locke's impossibility of telling "which was the globe and which the cube," but do show some surprisingly effective vision from the start. There are, however, marked problems such as failing to see depth correctly, failing to connect features through gaps, and unusual theory-suggestive responses to illusion figures of various kinds. SB saw a drawn Necker Cube as flat and without the usual flipping in depth. MM also saw the figure as flat, though a rotated simulated wire cube jumped into depth.

Although MM's visual acuity was limited cortically, and his perceptual form and face recognition—along with the brain activity such vision evoked—were poor, his brain activity evoked by motion stimuli was nearly normal (**Fig. 1a**). The new vision could be upsetting. MM had been a champion blind skier (**Fig. 1b**), but immediately after his operation he would close his functional eye when skiing down a slope. This was paralleled by SB becoming terrified by oncoming traffic when sighted, though when blind he would raise his stick and charge across the street unconcerned.

Returning to illusions, another marked similarity of SB and MM is their reduced susceptibility to certain illusory distortions. This is evidently due to loss of 'constancy scaling,' the perceptual compensation for shrinking of retinal images with increased object distance, as signaled by perspective or other depth cues. Such deficits in SB originally suggested inappropriate constancy as an explanation for distortion illusions[5]. Along the same lines, MM has difficulty seeing illusory contours in Kanizsa figures. This may be related to the electrophysiological finding that these beautiful phenomena do not originate at the first stage of visual processing (V1), but later in the visual system.

Many, if not all, historical cases have sad endings involving severe depression. This may be due to disappointed expectations when seeing is not fully gained, or it may simply be too confusing. This new case of MM seems to be exceptional, perhaps because of his high intelligence and optimistic temperament, and a happy marriage to the lady who helped him ski while blind. He continues to show improved vision as his knowledge increases. This would have pleased John Locke—who would be amazed that human understanding now extends to seeing what is happening physically in the head.

MM should give encouragement to future blind people who are able to take this extraordinary step from their familiar world of blindness to delayed sight. There are dangers: SB felt successful and contented as a blind man, but became miserable when partially sighted. MM seems to show it is possible to live happily with delayed sight, and to gain from the new experiences. But it takes unusual courage to venture into the world of sight from blindness, and it requires imaginative help from family and friends for a blind person to join them in their world.

1. Fine, I. *et al. Nat. Neurosci.* **6**, 915–916 (2003).
2. Locke, J. *Essay Concerning Human Understanding* Book II, Ch. 9. Sect. 8 (1694) (ed. Nidditch, P.) (Oxford Univ. Press, 1975).
3. von Senden, M. *Space and Sight: the Perception of Space and Shape in the Congenitally Blind Before and After Operation* (1932) (Methuen, London, 1960).
4. Gregory, R.L. & Wallace, J.G. Recovery from early blindness: a case study. *Qu. J. Exp. Psychol.* Monograph 2. (Heffers, Cambridge, 1963).
5. Gregory, R.L. *Nature* **199**, 678–691 (1963).