6. Revenkova, E., Herrmann, K., Adelfalk, C., and Jessberger, R. (2010). Oocyte cohesin expression restricted to pre-dictyate stages provides full fertility and prevents aneuploidy. Curr. Biol. *20*, 1529–1533.
7. Chiang, T., Duncan, F.E., Schindler, K., Schultz, R.M., and Lampson, M.A. (2010). Evidence that weakened centromere cohesin is a leading cause of age-related aneuploidy in oocytes. Curr. Biol. *20*, 1522–1528.
8. Lister, L., Kouznetsova, A., Hyslop, L., Kalleas, D., Pace, S., Barel, J., Nathan, A., Floros, V., Adelfalk, C., Watanabe, Y., *et al*. (2010). Age-related meiotic segregation errors in mammalian oocytes are preceded by depletion of cohesin and Sgo2. Curr. Biol. *20*, 1511–1521.
9. Suja, J.A., and Barbero, J.L. (2009). Cohesin complexes and sister chromatid cohesion in mammalian meiosis. Genome Dyn. *5*, 94–116.
10. Wood, A.J., Severson, A.F., and Meyer, B.J. (2010). Condensin and cohesin complexity: the expanding repertoire of functions. Nat. Rev. Genet. *11*, 391–404.
11. Sakuno, T., and Watanabe, Y. (2009). Studies of meiosis disclose distinct roles of cohesion in the core centromere and pericentromeric regions. Chromosome Res. *17*, 239–249.
12. Revenkova, E., Eijpe, M., Heyting, C., Hodges, C.A., Hunt, P.A., Liebe, B., Scherthan, H., and Jessberger, R. (2004). Cohesin SMC1 beta is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. Nat. Cell Biol. *6*, 555–562.
13. Hodges, C.A., Revenkova, E., Jessberger, R., Hassold, T.J., and Hunt, P.A. (2005). SMC1beta-deficient female mice provide evidence that cohesins are a missing link in age-related nondisjunction. Nat. Genet. *37*, 1351–1355.
14. Subramanian, V.V., and Bickel, S.E. (2008). Aging predisposes oocytes to meiotic nondisjunction when the cohesin subunit SMC1 is reduced. PLoS Genet. *4*, e1000263.
15. Hassold, T., and Hunt, P. (2009). Maternal age and chromosomally abnormal pregnancies: what we know and what we wish we knew. Curr. Opin. Pediatr. *21*, 703–708.
16. Oliver, T.R., Feingold, E., Yu, K., Cheung, V., Tinker, S., Yadav-Shah, M., Masse, N., and Sherman, S.L. (2008). New insights into human nondisjunction of chromosome 21 in oocytes. PLoS Genet. *4*, e1000033.
17. Hodges, C.A., Ilagan, A., Jennings, D., Keri, R., Nilson, J., and Hunt, P.A. (2002). Experimental evidence that changes in oocyte growth influence meiotic chromosome segregation. Hum. Reprod. *17*, 1171–1180.
18. Perez, G.I., Jurisicova, A., Wise, L., Lipina, T., Kanisek, M., Bechard, A., Takai, Y., Hunt, P., Roder, J., Grynpas, M., *et al*. (2007). Absence of the proapoptotic Bax protein extends fertility and alleviates age-related health complications in female mice. Proc. Natl. Acad. Sci. USA *104*, 5229–5234.
19. Garcia-Cruz, R., Brieno, M.A., Roig, I., Grossmann, M., Velilla, E., Pujol, A., Cabero, L., Pessarrodona, A., Barbero, J.L., and Garcia Caldes, M. (2010). Dynamics of cohesin proteins REC8, STAG3, SMC1{beta} and SMC3 are consistent with a role in sister chromatid cohesion during meiosis in human oocytes. Hum. Reprod. *25*, 2316–2327.
20. Hassold, T., and Chiu, D. (1985). Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. Hum. Genet. *70*, 11–17.

School for Molecular Biosciences, Washington State University, WA 99164, USA.
*E-mail: pathunt@wsu.edu

DOI: 10.1016/j.cub.2010.08.011

Visual System: How Does Blindsight Arise?

Some patients can discriminate unseen visual stimuli within a field defect caused by damage to the primary visual cortex. The pathways for this 'blindsight' have never been established, but recent studies implicate hitherto overlooked cells in the thalamic LGN.

Alan Cowey

The primary visual cortex, or V1, is the major cortical destination of the input from the eyes and contains a 'map' of the image on the retina. Hardly surprising, then, that when it is partly destroyed, as often happens following stroke or traumatic injury to the back of the brain, the patient has a visual field defect in which he is clinically blind — part of the map has been deleted. Why the term 'clinically blind'? Why not just blind? The answer lies in a controversy that began almost a century ago between two eminent British neurologists. Gordon Holmes [1] concluded that, in the absence of part of the striate cortex, the blindness is complete, the field defect is absolute. But George Riddoch [2], contemporary and colleague, disagreed and argued that such patients could perceive motion within their otherwise blind field. This controversy, like old volcanoes, has rumbled on ever since and pervades much of the research on what is now called blindsight.

Several investigators have studied the role of V1 in monkeys, the visual pathways of which closely resemble our own. They have found an ever increasing range of residual visual sensitivity and discrimination within the visual field defect caused by removing part, or even all, of V1 (see [3] for review) — not just reflexes such as the pupillary response to light, but also learned voluntary responses to the orientation, shape, brightness, size and motion of visual stimuli. Unsurprisingly, monkeys, unlike human patients, were considered to have genuine residual vision and this was attributed to the many other pathways from the eye into the brain, as shown schematically in Figure 1.

But a huge puzzle remained: why don't patients have the same abilities given that they too have these other pathways? The answer lies in the different ways in which monkeys and patients had been tested for decades. Patients were asked whether they saw anything in their field defects and with the exception of motion — and perhaps not even that — they said "No". But monkeys were not asked this question. Instead, and in order to get a reward, they had to choose between two visual stimuli — to make forced-choice decisions. This difference was highlighted when several investigators [4,5], using forced-choice guessing, demonstrated that patients were just as good as monkeys, and Cowey and Stoerig [6] showed that monkeys categorized visual stimuli that they could detect as being not like a light, but invisible. In both cases the subjects were showing 'blindsight', excellent forced choice performance in the face of denial of consciously seeing anything.

Once the relevance of investigations on monkeys to human blindsight was established the search was renewed in monkeys for the pathways that underlie it. Did all the pathways shown in Figure 1 contribute or only one or a few? Early work [7] showed that monkeys with part of V1 removed could still move their eyes to targets confined to the field defect but that this ability was destroyed if the corresponding part of the superior colliculus, which also has a 'map' of the retina, was subsequently extirpated. This still remains strong evidence that the pathway from the eye to the superior

colliculus [8], and perhaps onwards from there — which consists of more than 10^4 fibres from each eye — is responsible for blindsight, a conclusion that anatomical demonstrations of other pathways from eye to cortex that do not involve the superior colliculus have done little to modify. The recent paper by Schmid and colleagues [9] is bound to rekindle this debate. By combining behavioural, functional neuroimaging, and neuropharmacological methods, these authors provide the most compelling evidence yet that a direct pathway from the retina to the thalamic lateral geniculate nucleus (LGN), and from there to extrastriate visual cortex, is the key to understanding blindsight.

The LGN has sometimes been likened to a jumbo club sandwich. It has six prominent layers of neurons, shown in Figure 2. The top 4, called 'parvocellular' because the neurons are small, receives input from the colour-opponent P ganglion cells of the eyes. The two bottom, 'magnocellular' layers receive their input from the retinal M ganglion cells, which are not colour opponent, or only slightly so. Almost every P and M cell in the LGN, about a million of them, degenerates within a few weeks of removing V1. It was previously assumed that all blindsight must therefore derive from the retinal ganglion cells that project to the midbrain, as shown in Figure 1.

But what about the layers of the LGN between the P and M layers? In these interlaminar layers, the cells are small and so pale in conventional Nissl stained sections that they were mistaken for interneurons or non-neuronal glial cells by many investigators for many years. That this was incorrect became clear only 10 years ago [10] with the discovery that the K, or 'konio' retinal cells project to these interlaminar layers, the cells of which are as abundant as the large conspicuous M cells of the LGN. Moreover, they do *not* degenerate, or not extensively, after V1 is damaged. Furthermore, the K cells of the interlaminar layers project to extrastriate visual cortex [11], bypassing V1. These discoveries set the stage for the recent investigations by Schmid *et al.* [9,12].

Using awake behaving monkeys, Schmid *et al.* first showed [12] that, within a field defect caused by removing part of V1, the monkeys could still detect and move their eyes to visual stimuli confined to the field

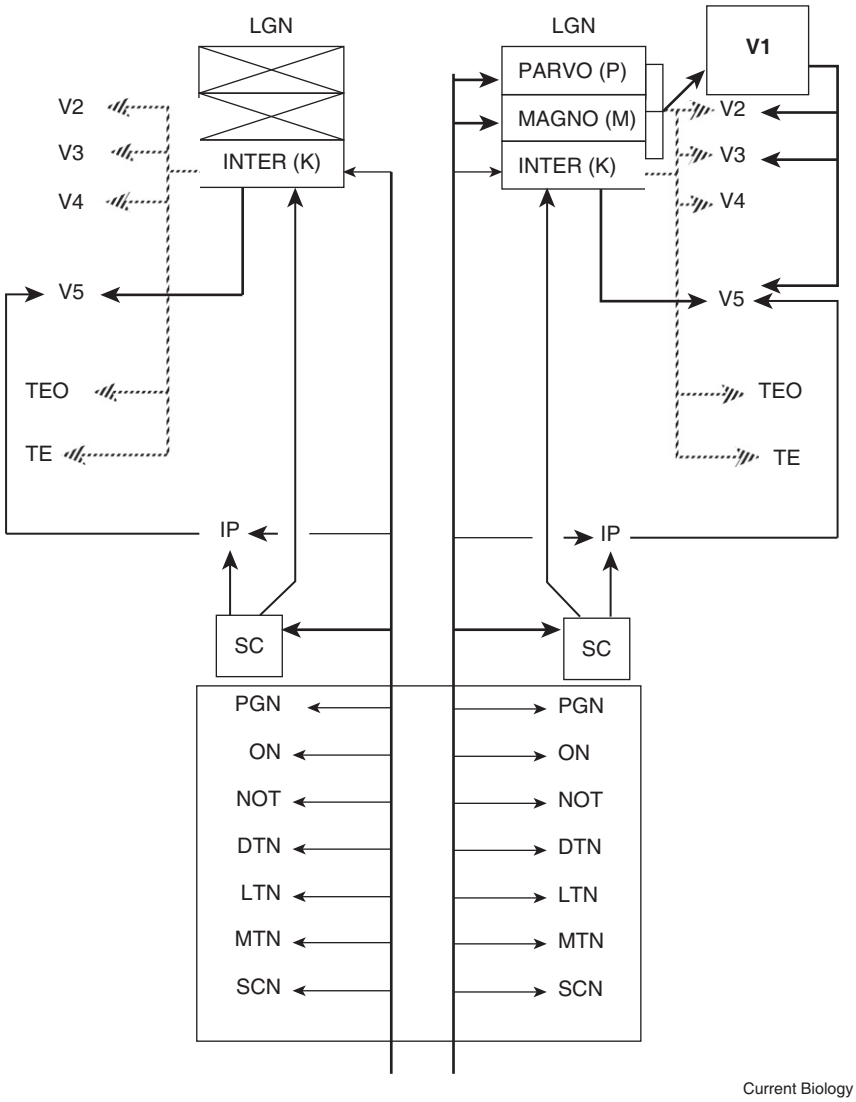

Figure 1. The known pathways from the eye to the brain.

The right side of the diagram shows the normal arrangement; the left side shows the effect of removing V1. Thicker lines show the heavier projections. Dotted lines show numerically weaker projections. The many onward cortical pathways from V2, V3, V4, etc. are omitted. On the left, lacking V1, the major visual input to the temporal lobe processing stream is diminished but that from the K cells remains. The subcortical nuclei within the square outline at the bottom are chiefly concerned with reflexive responses to light. Labelling from bottom upwards: SCN, suprachiasmatic nucleus; MTN, LTN and DTN, medial, lateral and dorsal terminal accessory optic nuclei; NOT, nucleus of the optic tract; ON, olivary nucleus; PGN, pregeniculate nucleus; SC, superior colliculus; IP, inferior pulvinar; LGN, lateral geniculate nucleus. It is not yet clear whether the K cell input to temporal lobe areas TEO and TE is direct or via V2, V3 and V4. Adapted with permission from [3].

defect, initially shown many years ago [7,13]. But, for the first time, they found that neurons in the extrastriate visual areas V2 and V3 were excited by the stimuli, albeit sub-normally. This extended earlier observations [13,14] that cells in the motion area MT^+/V5 of similar monkeys were also excitable by moving visual stimuli within a field defect and demonstrated that the blind-field responses were not restricted to the extrastriate motion areas.

The most recent study [9] of two macaque monkeys with field defects produced by V1 lesions goes much further by functional magnetic resonance imaging (fMRI) of the monkeys while they are discriminating visual stimuli in the scanner. The functional images showed that extrastriate visual areas V2, V3, V4, MT^+/V5, the floor of the superior temporal sulcus and parts of the parietal lobe were all activated by visual

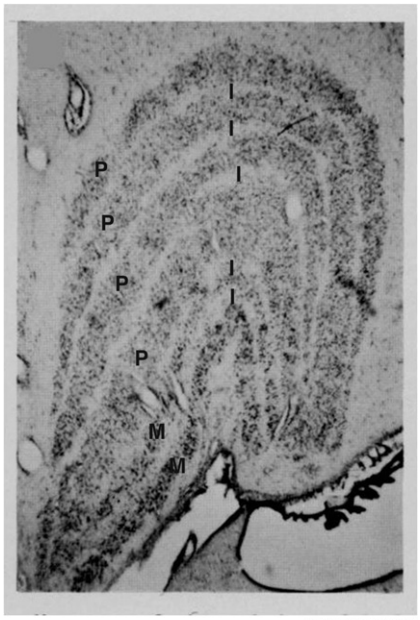

Figure 2. Nissl stained section through a normal macaque monkey's LGN.

P, parvocellular layers; M, magnocellular layers; I, interlaminar layers. Adapted with permission from [17].

stimuli in the field defect. But when the lateral geniculate nucleus was reversibly inactivated by the GABA agonist THIP — the effective region of which was visualised by concurrent structural magnetic imaging and by also injecting the magnetic resonance contrast-agent gadolinium — both the extrastriate activity and the behavioural discrimination were abolished.

As the GABA agonist does not affect the retinal axons passing beneath the LGN *en route* to the superior colliculus, the role of the latter and other mid-brain centres in blindsight has to be re-evaluated. Further steps are likely to include whether the pathway from eye to superior colliculus is indeed important but that the output from superior colliculus is routed via the interlaminar layers of the LGN. It will also be important to record from the amygdala, often implicated in affective blindsight [15,16] such as responses to emotional visual stimuli, in order to determine whether the amygdala has a privileged visual input that is independent of the LGN and might involve the collicular projections to the pulvinar nucleus and/or the medial dorsal thalamus. Lastly, as icing on the cake, it should be possible to demonstrate behaviourally that such monkeys are displaying blindsight when they respond. It seems that the resolution of a longstanding problem is at last in sight.

References

1. Holmes, G. (1918). Disturbances of vision caused by cerebral lesions. Brit. J. Ophthalmol. *2*, 353–384.
2. Riddoch, G. (1917). Dissociations of visual perceptions due to occipital injuries, with especial reference to appreciation of movement. Brain *40*, 15–57.
3. Stoerig, P., and Cowey, A. (1997). Blindsight in man and monkey. Brain *120*, 535–559.
4. Pöppel, E., Frost, D., and Held, R. (1973). Residual visual function after brain wounds involving the central visual pathways in man. Nature *243*, 295–296.
5. Weiskrantz, L., Warrington, E.K., Sanders, M.D., and Marshall, J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. Brain *97*, 709–728.
6. Cowey, A., and Stoerig, P. (1995). Blindsight in monkeys. Nature *373*, 247–249.
7. Mohler, C.W., and Wurtz, R.H. (1977). Role of striate cortex and superior colliculus in the guidance of saccadic eye movements in monkeys. J. Neurophysiol. *40*, 74–94.
8. Cowey, A., and Stoerig, P. (1991). The neurobiology of blindsight. Trends Neurosci. *14*, 140–145.
9. Schmid, M.C., Mrowka, S.W., Turchi, J., Saunders, R.C., Wilke, M., Peters, A.J., Ye, F.Q., and Leopold, D.A. (2010). Blindsight depends on the lateral geniculate nucleus. Nature *466*, 373–377.
10. Hendry, S.H.C., and Reid, R.C. (2000). The koniocellular pathway in primate vision. Annu. Rev. Neurosci. *23*, 127–153.
11. Sincich, L.C., Park, K.F., Wohlgemuth, M.J., and Horton, J.C. (2004). Bypassing V1: a direct geniculate input to area MT. Nat. Neurosci. *7*, 1123–1128.
12. Schmid, M.C., Panagiotaropoulos, T., Augath, M.A., Logothetis, N.K., and Smirnakis, S.M. (2009). Visually driven activation in macaque areas V2 and V3 without input from the primary visual cortex. PLoS ONE *4*, e5527.
13. Moore, T., Rodman, H.R., Repp, A.B., and Gross, C.G. (1995). Localization of visual stimuli after striate cortex damage in monkeys: Parallels with human blindsight. Proc. Natl. Acad. Sci. USA *92*, 8215–8218.
14. Azzopardi, P., Fallah, M., Gross, C.G., and Rodman, H.R. (2003). Response latencies of neurons in visual areas MT and MST of monkeys with striate cortex lesions. Neuropsychologia *41*, 1738–1756.
15. Pegna, A.J., Khateb, A., Lazeyras, F., and Seghier, M.L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. Nat. Neurosci. *8*, 24–25.
16. Gonzalez-Andino, S.L., Grave de Peralta Menendez, R., Khateb, A., Landis, T., and Pegna, A.J. (2009). Electrophysiological correlates of affective blindsight. NeuroImage *44*, 581–589.
17. Cowey, A., Stoerig, P., and Williams, C. (1999). Variance in transneuronal retrograde ganglion cell degeneration in monkeys after removal of striate cortex: effects of size of the cortical lesion. Vision Res. *39*, 3642–3652.

University of Oxford, Department of Experimental Psychology, South Parks Road, Oxford OX1 3UD, UK.
E-mail: Alan.Cowey@psy.ox.ac.uk

DOI: 10.1016/j.cub.2010.07.014

Gene Silencing: Small RNAs Control RNA Polymerase II Elongation

Short interfering RNAs trigger histone silencing marks and stalling of RNA polymerase II at their genomic target sites through a mechanism termed transcriptional gene silencing (TGS). The Argonaute protein NRDE-3, along with NRDE-2, are needed for TGS in *C. elegans*. TGS also inhibits elongation and controls alternative splicing in mammalian cells.

Mariano Alló and Alberto R. Kornblihtt*

Three types of small, double-stranded RNAs play fundamental regulatory roles in eukaryotic cells. Although they share many functions, these RNAs differ in length, internal complementarity, protein partners and mechanisms of action. Whereas short interfering RNAs (siRNAs) and microRNAs (miRNAs) are 21–25 nucleotides long, PIWI-interacting RNAs (piRNAs) are 24–31 nucleotides long. The two strands of siRNAs and piRNAs are fully complementary, while a distinctive feature of miRNAs is the presence of internal mismatches. All three types are able to trigger degradation or translational arrest of mRNAs carrying target sequences in a cytoplasmic process known as post-transcriptional gene silencing (PTGS). PTGS elicited by transfection of siRNAs targeting specific mRNAs has become one of the most powerful tools to knockdown gene expression in mammalian cells and study gene function in a rapid, affordable and robust way. A second mechanism triggered by small RNAs, termed transcriptional gene silencing (TGS), is