False perception of motion in a patient who cannot compensate for eye movements

Thomas Haarmeier, Peter Thier, Marc Repnow & Dirk Petersen*

*Section on Sensorimotor Research, Department of Neurology, and * Department of Neuroradiology, University of Tübingen, 72076 Tübingen, Germany*

We are usually unaware of the motion of an image across our retina that results from our own movement. For instance, during slow-tracking eye movements we do not mistake the shift of the image projected onto the retina for motion of the world around us, but instead perceive a stable world. Following early suggestions by von Helmholtz[1], it is commonly believed that this spatial stability is achieved by subtracting the retinal motion signal from an internal reference signal, such as a copy of the movement command (efference copy)[2–4]. Object motion is perceived only if the two differ. Although this concept is widely accepted, its anatomical underpinning remains unknown. Here we describe the case of a patient with bilateral extrastriate cortex lesions, suffering from false perception of motion due to an inability to take eye movements into account when faced with self-induced retinal image slip. This is indicated by the fact that during smooth-pursuit eye movements, he perceives motion of the stationary world at a velocity that corresponds to the velocity of his eye movement; that is, he perceives the raw retinal image slip uncorrected for his own eye movements. We suspect that this deficiency reflects damage of a distinct parieto-occipital region that disentangles self-induced and externally induced visual motion by comparing retinal signals with a reference signal encoding eye movements and possibly ego-motion in general.

R.W., a 35-year-old male, was admitted to our hospital in August 1996. He complained of vertigo and nausea that he had been experiencing for more than 6 years. Vertigo in this patient occurs either with the eyes tracking moving objects (for example watching his children on a carousel or playing computer games that require the observation of moving targets) or with the eyes fixed on a stationary object during translational ego-motion (such as watching objects through the lateral window of a moving car or train). It promptly disappears when the eyes are closed. On careful neurological examination, no abnormality was found except for a slight reduction in visual acuity of the left eye (see Methods for clinical details). Magnetic resonance imaging (MRI) revealed bilateral extrastriate cortex lesions (Fig. 1). The specific conditions under which vertigo in R.W. occurs led us to assume that it was selectively related to the processing of visual motion induced by ego-motion. In order to verify this hypothesis, we performed detailed psychophysical tests assessing R.W.'s perception of self-induced visual motion resulting from his smooth-pursuit eye movements.

Whenever smooth pursuit is carried out across a stationary background, the resulting slip of the background image on the retina has to be related to the eye movement in order not to be misinterpreted as background motion. According to the inferential theory of perception, visual stability during pursuit eye movements is the result of the comparison of a signal that reflects retinal image slip with an internal reference signal that encodes the eye movement[1–4]. If this comparison were perfect, no pursuit-induced background movement would be perceived. However, although our visual system comes close to this ideal (see below), slight imperfections can be revealed in the form of the perception of a tiny and usually non-disturbing movement of the stationary world. This illusionary background motion induced by pursuit eye movements is commonly referred to as the Filehne illusion[5]. The Filehne illusion can be measured by determining the amount of external background motion required to compensate for it, thus yielding the impression of a stationary background. At this point of subjective stationarity (PSS), the physical background motion is equal in magnitude and opposite to the direction of the Filehne illusion[6]. The smaller the illusion, the better our ability to cope with self-induced retinal image slip. Using a two-alternative forced choice paradigm with varying background velocities, we identified the PSS for horizontal pursuit eye movements as the one giving on average as many left as right responses[7]. In accordance with our previous work using similar stimulation conditions[7,8], our measurements revealed that the illusionary motion perceived was indeed almost negligible in healthy subjects ($n = 18$) whose mean age matched that of R.W. This was indicated by the fact that background velocity at the PSS was close to 0 deg s^{-1} over a broad range of eye velocities tested (Fig. 2). In R.W., however, stimulus velocity at the PSS was dramatically increased (Fig. 2) and moreover was dependent on the eye velocity prevailing. Despite a considerable variability in his performance, there was a clear tendency towards higher Filehne

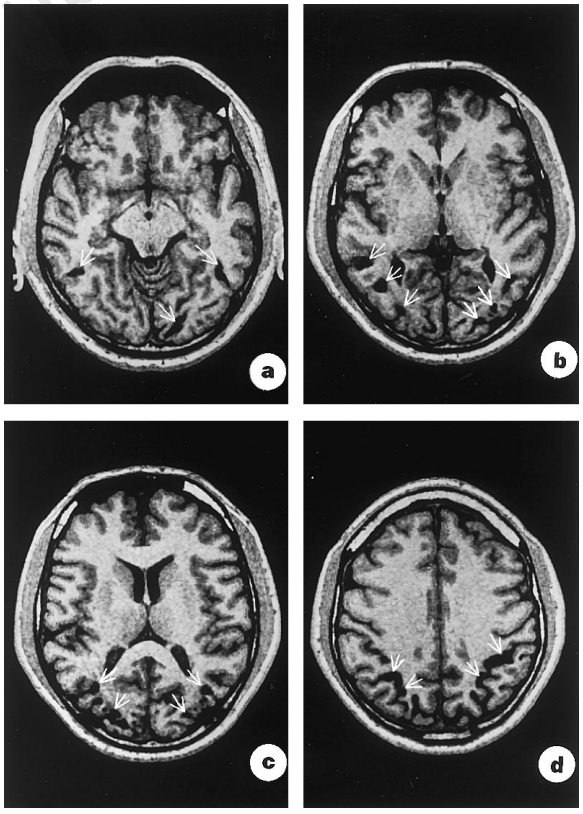

Figure 1 MRI shows bilateral cyst-like local widenings (arrows) of the sulci of the occipital lobe mainly affecting parts of areas 18, 19 and possibly 37 on the lateral aspect of the hemispheres and areas 18 and 19 on the inferior aspect (**a**–**c**). In addition, cortex in and around the intraparietal sulcus of the parietal lobes is involved (**d**). Axial 0.9-mm reconstructions parallel to the line connecting the anterior and posterior commissures (AC–PC line) are calculated from a high-resolution T1-weighted three-dimensional data set (3D-FLASH 30°, TR/TE = 30/5 ms, 1.5 tesla). T2-weighted images (not shown) were also consistent with sulcal widenings containing CSF. The lesions represent strictly cortical defects and local cortical atrophy without signs of progression. Subcortical white matter and basal ganglia are intact. Although the lesional pattern does not allow a definitive pathogenetic assignment, post-hypoxic cortical laminar necrosis seems to be most likely. As a possible cause, R.W. had suffered from a severe pertussis infection in early childhood which had required artificial respiration.

illusions with increasing eye velocities. Specifically, the linear regression plotted in Fig. 2 implies that R.W. did not perceive 'stationarity' unless background stimulus velocity roughly equalled target velocity—that is, unless the background image was stabilized on his retina.

In a first set of control experiments, we investigated whether R.W. suffered from a general deficit in retinal motion analysis also present in the absence of eye movements. We measured R.W.'s perception of visual motion that was not a consequence of self-motion but was instead due to motion in the environment. These tests, performed under stationary fixation, did not reveal any deficiency. Specifically, R.W. was as successful in detecting coherent motion in a random dot display[9] as were normal controls (Fig. 3a). His ability to extract a two-dimensional shape from motion, as assessed by a motion-defined letter test[10], was also unimpaired (motion threshold 0.093 deg s^{-1} as compared to a normal limit of 0.11 deg s^{-1} (refs 10, 11)). R.W. was also able to use retinal motion information to generate smooth eye movements, compensating for target motion, as indicated by pursuit eye movements of normal latency and gain (Fig. 3b). As a perceptual consequence of his intact smooth-pursuit eye movements, the acuity for moving Landolt targets (recently shown to be highly susceptible to even slight smooth-pursuit deficits[12]) was excellent in R.W. (binocular acuity was 1.0 both for a stationary Landolt target and a Landolt target moving at speeds of up to 12 deg s^{-1}). In summary, these results suggested that R.W.'s ability to analyse object-induced retinal image motion for perceptual as well as for oculomotor purposes was unimpaired.

R.W. is, moreover, by no means generally impaired on motion analysis during ego-motion. If efferent information such as a signal encoding the eye movement is not required, his performance is normal. This conclusion is suggested by an experiment, in which we measured R.W.'s ability to detect a change in the velocity of the pursuit target. This task can be performed successfully by detecting the retinal image slip resulting from the change in target velocity. Indeed, R.W.'s sensitivity thresholds for both acceleration and deceleration of the pursuit target were indistinguishable from those of controls ($n = 6$, Fig. 4).

In summary, our observations on R.W. show that the ability to perceive a stationary world, despite self-induced visual motion, can be selectively impaired as a consequence of an extrastriate cortex lesion. R.W. interprets retinal image slip as object motion in extrapersonal space, irrespective of whether it results from motion in the environment or, alternatively, from his pursuit eye movements. Because retinal analysis of object motion is normal in R.W., it must be the necessary comparison with an internal signal encoding the eye movement, which is impaired. Either the appropriate reference signal is missing or the comparison itself may no longer be

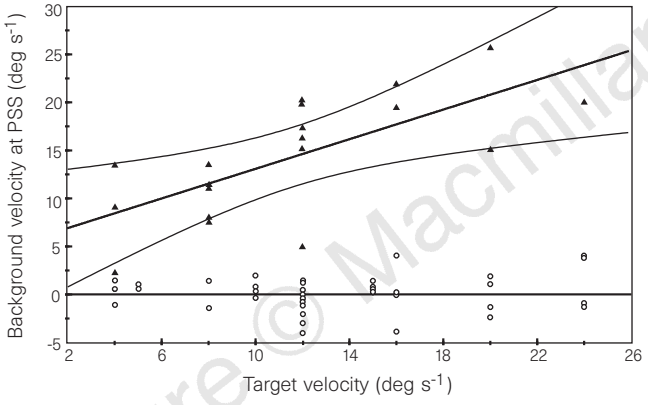

Figure 2 Perception of pursuit-induced visual motion in patient R.W. (filled triangles) and 18 control subjects (50 individual measurements represented by open circles, partially lying on top of each other). The background stimulus velocity that is perceived as stationary (PSS, point of subjective stationarity), that is, the estimate of the Filehne illusion, is plotted for the different pursuit target velocities varied from 4 to 24 deg s^{-1}. Target motion was always to the right. Positive values of background velocity at PSS indicate background movement in the same direction as the eyes. The higher the background velocity at PSS, the less the resulting retinal image slip velocity allowing the percept of stationarity and, thus, the less the ability to cope with self-induced visual motion. In the control subjects stimulus velocity at PSS is always close to 0 deg s^{-1}. Hence perceived background motion is tightly related to visual motion in extrapersonal space, that is, stationarity is preserved despite increasing retinal image shifts with growing target velocities. In R.W., however, perceived motion reflects image movement on the retina. The linear regression (with 99% confidence bands) suggests that R.W. is deprived of a sense of stationarity unless the background image is stabilized to some degree on his retina. Accordingly, he will experience Filehne illusions in the order of the eye velocity prevailing.

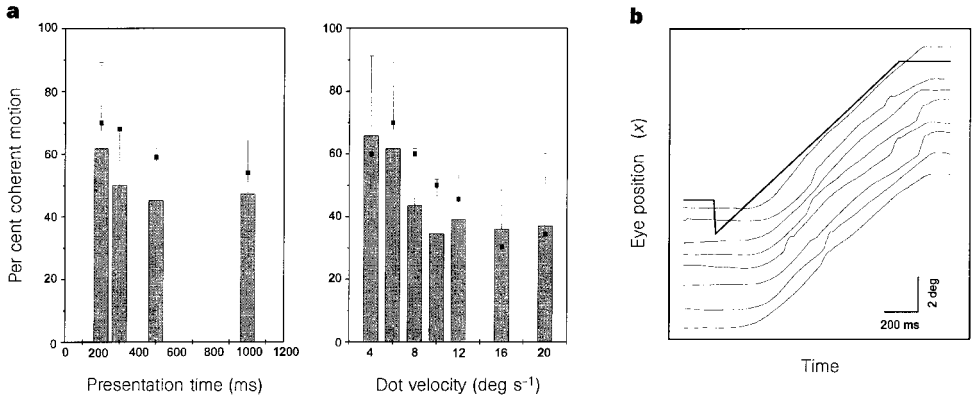

Figure 3 Evidence for unimpaired analysis of retinal motion in patient R.W. **a**, Detection of coherent visual motion in a random dot display. Threshold values of per cent coherence as function of stimulus presentation time (left panel, dot velocity, 6 deg s^{-1}) and dot velocity (right panel, presentation time, 200 ms), respectively. The results obtained from R.W. (represented by single bars) as compared to a group of 12 healthy controls (means/standard deviations) reveal no deficit and further show the same dependency on the two parameters varied. **b**, Records of individual trials of smooth-pursuit eye movements elicited using a step-ramp paradigm (step amplitude, 2 deg; ramp velocity, 10 deg s^{-1}). Eye movements were recorded with a high-resolution infrared reflection system at a sampling frequency of 200 Hz. Horizontal ramps to the right (upper four trials) and left (lower four trials) were unpredictably intermingled. Only the *x*-components of eye position are depicted.

possible. In either case, the location of the bilateral lesions revealed by MRI suggests that neural networks contributing to this comparison are located in the parieto-occipital lobe. This conclusion is in line with our recent demonstration of a parieto-occipital event-related potential that reflects the percept of self-induced visual motion[8]. We propose that the region destroyed in patient R.W. may involve cortex homologous to monkey area MST[13,14], and moreover that the functional deficit may be a direct consequence of this loss. The reason is that single-unit studies on monkeys have suggested that the ability to ignore self-induced retinal image slip might be confined to this late stage of cortical processing of visual motion while being absent in earlier stages including area V5[15,16]. The precise localization of human area MST is still a matter of debate. However, there is little doubt that it must lie immediately adjacent to human motion processing area V5, whose location close to the ascending limb of the inferior temporal sulcus is well established[17,18]. This region is part of the lesions in R.W., which therefore most probably not only involve putative human area MST but also area V5. In view of the probable involvement of V5, our finding of a normal analysis of retinal image motion, a function generally attributed to area V5, is puzzling. A possible explanation of this seeming paradox is offered by the fact that R.W. acquired the lesions probably in his early childhood, possibly early enough to allow spared elements of cortical motion processing to step in. Indeed, R.W. would not suffer from vertigo if the cortical processing of retinal image slip had not been maintained. □

Methods

Clinical details. Although R.W. described vertigo and nausea only for the past 6 years, his history revealed several peculiarities that suggest that he had been suffering from a loss of visual stability for a much longer time, possibly since his early childhood. For instance, he had never tried to acquire a driver's licence because he had been insecure in judging speed or distance of objects when travelling at high velocities, and during childhood, a striking insufficiency in ball games had always been in exceptional contrast to above-average results in athletics. Of course, both the analysis of external objects during car driving as well as the pursuit of balls in ball games involve goal-directed eye movements and consequently the need to handle self-induced retinal image slip.

On examination, the common causes of vertigo, such as peripheral or central vestibular dysfunction, were carefully excluded. For instance, there was no hearing loss, tinnitus or any kind of nystagmus. Caloric testing did not reveal any asymmetry in response and the vestibulo-ocular reflex was normal in terms of gain and phase. Pursuit eye movements, saccades and optokinetic nystagmus were intact, both clinically and on electronystagmographic recording. Electroencephalography demonstrated no focal slowing or paroxysmal discharge and thus provided no electrophysiological correlate of vestibular epilepsy. Moreover, R.W.'s failure to account for self-induced retinal motion was highly selective because other visual functions did not reveal any relevant disturbance. Specifically, no visual field defect was found in perimetric tests and colour vision, as assessed by Ishihara plates, was unimpaired. The only irregularity found was a slight reduction in acuity for the left eye (0.8 as compared to 1.0 for the right eye, resulting in a binocular acuity of 1.0). It had been attributed to a mild convergent strabism, which was surgically corrected in August 1995.

Psychophysical tests. With the exception of the motion-defined letter test (refs 10, 11; see ref. 11 for the specific parameters chosen), all other psychophysical tests followed an adaptive staircase procedure (PEST)[19], forcing the observer to select one of two alternative responses in the individual trial. Thresholds, as defined below, were determined by means of a probit analysis[20] with subsequent chi-square goodness-of-fit tests performed on the responses obtained from at least 40 trials in each session. Stimuli were presented on a 19-in computer monitor (Mitsubishi, frame rate 72 Hz, 1,280 × 1,024 pixel) in a dark (Filehne illusion, detection of velocity steps) or a brightly lit (static and dynamic visual acuity, coherent motion stimuli) experimental room. Viewing distance was 225 cm for the acuity measurements and 57 cm in the other experiments. During all tests, eye movements were monitored using an infrared iris reflection system (Amtech). Recordings were stored and analysed on-line at a sampling rate of 72 Hz by a workstation which also controlled the presentation of the stimuli. Deviations of eye position from the position of the given target exceeding 2 deg were fed back acoustically as errors and the corresponding trials were discarded. Off-line analysis of the recordings revealed no difference in oculomotor performance obtained from R.W. as compared to the control groups. Specifically, eye velocity was always within the range of group means +/− one standard deviation, and hence was verified not to account for any differences in the behavioural results.

Filehne illusion. Measurements of the Filehne illusions were performed as recently described by us[7]. Briefly, pursuit was elicited by a red dot (diameter 10 min of arc) which moved to the right at a constant velocity spanning a visual angle of 30 deg. Temporally located in the middle of the target sweep a background pattern was presented for 300 ms. This background stimulus subtended 27 × 27 deg of visual angle and consisted of 350 white dots (diameter 15 min of arc, local contrast 0.01). Subjects were asked to report the direction of perceived background motion which was varied by the psychophysical procedure. The PSS was defined as the background velocity that resulted in 50% left and 50% right responses after repeated presentation. Measurements started with the background stimulus velocity being 4 deg s^{-1} and were randomly interleaved with constant stimuli (−/+ 4 deg s^{-1}, respectively).

Coherent motion stimuli. The ability to detect coherent motion in a random dot field was tested by determining the minimum percentage of coherently moving dots required to discriminate this field from a second random dot field containing only non-coherently moving dots. The 2 random dot fields were borderless squares of 12 × 12 deg each and were presented simultaneously with their inner borders 2 deg left and right, respectively, of the fixation spot. Each random dot field contained 400 dots (diameter 7 min of arc, local contrast 0.1) moving at a specified velocity for a limited lifetime of 100 ms. For each trial a common direction of movement was chosen randomly between 0 and 360° for the coherently moving dots. The field containing coherent motion was chosen at random and the percentage of coherently moving dots was varied according to the adaptive staircase procedure. A coherence threshold was determined at which subjects responded correctly 75% of the time (where 50% correct is the

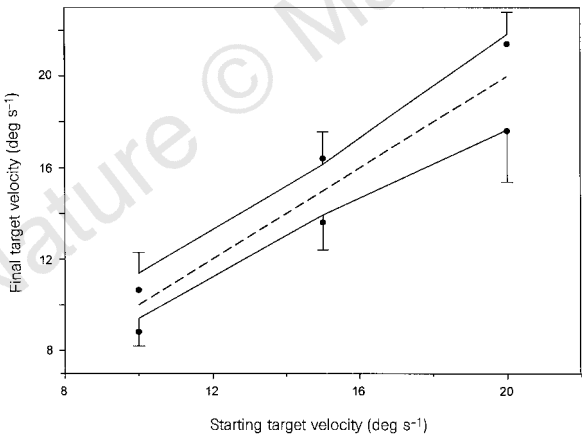

Figure 4 Performance of R.W. (dots) and 6 control subjects (means and standard deviations) on a task assessing the sensitivity to changes in the velocity of a moving target. The observers were instructed to track a target which started to move to the right at a fixed velocity, changed its velocity after a variable time interval and continued moving at the final speed for the rest of the target sweep. Using a two-alternative forced choice paradigm, thresholds were determined both for acceleration and deceleration by means of two separate staircase procedures running simultaneously within each session. The upper solid curve plots the final target velocity acquired after just perceptible accelerations, the lower solid curve the final target velocity after just perceptible decelerations of the target. The curves connect the mean thresholds for acceleration and deceleration, respectively, of the 6 controls. For the sake of clarity, standard deviations are plotted only for non-overlapping directions. The minimum perceptible acceleration and deceleration for a given starting target velocity can be deduced from this graph by measuring the deviation of the final target velocity from the starting target velocity (dashed line in between the two solid curves).

performance expected by chance). Presentation time and dot velocity were varied systematically as described in the results section. Note that several features of the design chosen make it more demanding than similar tests published[9], leading to comparatively high thresholds: these features involve the large number of dots, short dot lifetime, and particularly the need to compare two spatially separated random dot fields instead of detecting motion coherence in only one field.

Static and dynamic visual acuity. Resolution thresholds were measured both for stationary Landolt Cs (static visual acuity) and for moving Landolt Cs to be tracked by eye movements (dynamic visual acuity). Again, subjects had to press one of two buttons according to two possible positions of the Landolt C gap (either left or right) in this set of experiments. Optotypes were presented on a local background (white circle, luminance 60 cd m^{-2}, diameter equalling diameter of the Landolt C plus 2 × 20 min of arc) on an otherwise grey screen (luminance 7.8 cd m^{-2}). In the measurements of static acuity, trials started with a 500-ms presentation of the stationary local background followed by the Landolt C being visible for 250 ms. Dynamic acuity was determined using a ramp paradigm, with the local background moving in a rightward horizontal direction at a given velocity (visual angle 8 deg). Unpredictably within this sweep, the Landolt C was added to the local background and participated in the movement for 250 ms. Acuity thresholds were defined as the Landolt C gap resulting in 75% correct responses, spatial resolution of the monitor was enhanced by means of anti-aliasing techniques.

Detection of velocity steps. In this task the observers were instructed to track a target (diamond, length 10 min of arc, local contrast 0.1 as compared to the otherwise dark screen) which started to move to the right at a fixed velocity, changed its velocity after a variable interval (at least 800 ms) and continued moving at the final speed for another 500–1,400 ms (total ramp length, 30 deg). Subjects were asked to indicate whether the target had accelerated or decelerated during the sweep. Thresholds (defined by 75% right and left responses, respectively) were determined both for acceleration and deceleration by means of two separate staircase procedures running simultaneously within each session.

Received 26 June; accepted 22 August 1997.

1. von Helmholtz, H. *Physiological Optics* Vol. III (Dover, New York, 1962) (trans. from 3rd German edn of 1910).
2. von Holst, E. & Mittelstaedt, H. Das Reafferenzprinzip. *Naturwissenschaften* **37,** 464–476 (1950).
3. Sperry, R. W. Neural basis of the spontaneous optokinetic response produced by visual inversion. *J. Comp. Physiol. Psychol.* **43,** 482–489 (1950).
4. Wertheim, A. H. Motion perception during self-motion: the direct versus inferential controversy revisited. *Behav. Brain Sci.* **17,** 293–355 (1994).
5. Filehne, W. Über das optische Wahrnehmen von Bewegungen. *Z. Sinnesphysiol.* **53,** 134–145 (1922).
6. Mack, A. & Herman, E. Position constancy during pursuit eye movements: an investigation of the Filehne illusion. *Q. J. Exp. Psychol.* **25,** 71–84 (1973).
7. Haarmeier, T. & Thier, P. Modification of the Filehne illusion by conditioning visual stimuli. *Vis. Res.* **36,** 741–650 (1996).
8. Haarmeier, T. & Thier, P. An electrophysiological correlate of visual motion awareness in man. *J. Cogn. Neurosci.* (in the press).
9. Rizzo, M., Nawrot, M. & Zihl, J. Motion and shape perception in cerebral akinetopsia. *Brain* **118,** 1105–1127 (1995).
10. Regan, D., Kothe, A. C. & Sharpe, A. Recognition of motion-defined shapes in patients with multiple sclerosis and optic neuritis. *Brain* **114,** 1129–1155 (1991).
11. Herbst, H., Ketabi, A., Thier, P. & Dichgans, J. Comparison of psychophysical and evoked potential methods in the detection of visual deficits in multiple sclerosis. *Electroenceph. Clin. Neurophysiol.* **104,** 82–90 (1997).
12. Haarmeier, T. & Thier, P. Impaired dynamic visual acuity due to deficient smooth pursuit eye movements. *Soc. Neurosci. Abstr.* **23,** 1950 (1997).
13. Komatsu, H. & Wurtz, R. J. Relation of cortical areas MT and MST to pursuit eye movements. I. Localization and visual properties of neurons. *J. Neurophysiol.* **60,** 580–603 (1988).
14. Komatsu, H. & Wurtz, R. J. Relation of cortical areas MT and MST to pursuit eye movements. III. Interaction with full-field visual stimulation. *J. Neurophysiol.* **60,** 621–644 (1988).
15. Erickson, R. G. & Thier, P. A neuronal correlate of spatial stability during periods of self-induced visual motion. *Exp. Brain Res.* **86,** 608–616 (1991).
16. Ilg, U. J. & Thier, P. Inability of rhesus monkey area V1 to discriminate between self-induced and externally induced retinal image slip. *Eur. J. Neurosci.* **8,** 1156–1166 (1996).
17. Tootell, R. B. *et al.* Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci.* **15,** 3215–3230 (1995).
18. Zeki, S. *et al.* A direct demonstration of functional specialization in human visual cortex. *J. Neurosci.* **11,** 641–649 (1991).
19. Lieberman, H. R. & Pentland, A. P. Microcomputer-based estimation of psychophysical thresholds: the best PEST. *Behav. Res. Methods Instr.* **14,** 21–25 (1982).
20. McKee, S. P., Klein, S. A. & Teller, D. Y. Statistical properties of forced choice psychometric functions: implications of probit analysis. *Percept. Psychophy.* **37,** 286–298 (1985).

Acknowledgements. We thank patient R.W. for participating in our experiments. Supported by KFG 'Neuroophthalmologie'.

Correspondence and requests for materials should be addressed to P.T. (e-mail: hans-peter.thier@uni-tuebingen.de).

Ligand-induced changes in integrin expression regulate neuronal adhesion and neurite outgrowth

M. L. Condic* & P. C. Letourneau†

* *Department of Neurobiology and Anatomy, University of Utah, School of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132, USA*
† *Department of Cell Biology and Neuroanatomy, 4-135 Jackson Hall, 321 Church Street South-East, University of Minnesota, Minneapolis, Minnesota 55455, USA*

Receptors of the integrin family are expressed by every cell type and are the primary means by which cells interact with the extracellular matrix. The control of integrin expression affects a wide range of developmental and cellular processes, including the regulation of gene expression, cell adhesion, cell morphogenesis and cell migration[1–3]. Here we show that the concentration of substratum-bound ligand (laminin) post-translationally regulates the amount of receptor ($\alpha_6\beta_1$ integrin) expressed on the surface of sensory neurons. When ligand availability is low, surface amounts of receptor increase, whereas integrin RNA and total integrin protein decrease. Ligand concentration determines surface levels of integrin by altering the rate at which receptor is removed from the cell surface. Furthermore, increased expression of integrin at the cell surface is associated with increased neuronal cell adhesion and neurite outgrowth. These results indicate that integrin regulation maintains neuronal growth-cone motility over a broad range of ligand concentrations, allowing axons to invade different tissues during development and regeneration.

Cell migration is critical to the development of all embryonic tissues. For cell migration to occur, a precise balance must be maintained between adhesion to the substratum, which is necessary to generate mechanical force, and de-adhesion, which is required to change position. For many cell types[4–7], substratum-bound extracellular matrix (ECM) molecules support optimal motility over a very limited range of ECM surface densities. As the concentration of substratum-bound molecules or the number of cellular receptors increases, the strength of cell attachment to the substratum increases until cells are attached too strongly to migrate[8]. In contrast to other migratory cell types, neurons both *in vivo*[9] and *in vitro*[10] (Fig. 1a) extend neurites over a wide range of ECM ligand concentrations, suggesting that they regulate their degree of adhesion to the ECM. The capacity of sensory and motor neurons to regulate cell–matrix interactions requires that they have a mechanism for modulating either the expression or function of ECM receptors that is not seen in other non-invasive cell types. Neurons could alter their interactions with the matrix to preserve growth-cone motility either by changing receptor affinity[11] or by regulating the amount or the subcellular distribution of receptors. These possibilities can be distinguished by examining the number of ECM receptors that are expressed under conditions of high and low availability of ligand.

The hypothesis that neurons respond to low availability of a growth-promoting ECM ligand such as laminin by increasing their expression of receptor, thereby strengthening the interaction with the substratum, predicts that the levels of laminin receptor expressed by a neuron should increase when the amounts of substratum-bound laminin decrease. Dorsal root ganglion neurons were cultured overnight on substrata containing a tenfold difference in bound laminin or on fibronectin, as a control for the absence of laminin (Fig. 1b), and analysed for expression of integrin $\alpha_6\beta_1$ (the only laminin-specific integrin known to be expressed by sensory