skarn. This episode of flow was a singular event in the history of the belt, occurring during peak-grade metamorphism. It may have been triggered by the development of porosity when dolomite and quartz reacted to produce diopside cores in hitherto impermeable, internally buffered marble, and accelerated as dolomite then reacted with infiltrating water, giving rise to further secondary porosity[18,19]. Even with increased porosity, the kilometre-scale focused flow along fold hinges in the CMF is possible only if there are breakout points with rapid hydraulic connection to areas of relatively low fluid pressure, so that fluid is driven into the metasomatic conduits because fluid pressure is lower than in nearby beds. In an overpressured system, convective recharge and recirculation are then impossible[3].

A final question raised by the model illustrated in Fig. 4 is whether the type of abrupt fluid loss event we propose has implications for the rheological behaviour of the fold belt. The peak-metamorphic fold structures along the central axis of Connemara where the CMF occurs are rather less tight than those to north and south. Because deformation mechanisms in high-grade metamorphism are often fluid-dependent, the loss of fluid and fluid pressure, once flow through the marble conduits began, may have caused an increase in silicate rock strength, so that regional strain became progressively partitioned into those rocks sufficiently far from the marble aquifer that they remained unaffected by the fluid loss. Because metasomatic rocks are common in high-grade marbles, the implications of such a process may be very widespread. □

Received 30 April; accepted 15 November 1990.

1. Etheridge, M. A., Wall, V. J. & Cox, S. F. *J. geophys. Res.* **89,** 4344-4358 (1984).
2. Walther, J. V. & Orville, P. M. *Contr. Miner. Petrol.* **79,** 252-257 (1982).
3. Yardley, B. W. D. *Adv. phys. Geochem.* **5,** 109-131 (1986).
4. Rye, R. O., Schuiling, R. D., Rye, D. M. & Jansen, J. B. H. *Geochim. cosmochim. Acta* **40,** 1031-1049 (1976).
5. Ferry, J. M. *Am. Miner.* **72,** 39-58 (1987).
6. Nabelek, P. I., Hanson, G. H., Labotka, T. C. & Papike, J. J. *Contr. Miner. Petrol.* **99,** 49-61 (1988).
7. Baker, A. J. *J. Petrol.* **31,** 243-260 (1990).
8. Yardley, B. W. D., Barber, J. P. & Gray, J. R. *Phil. Trans. R. Soc.* A**321,** 243-270 (1987).
9. Tanner, P. W. G. & Shackleton, R. M. in *The Caledonides of the British Isles* (eds Harris, A. L., Holland, C. H. & Leake, B. E.) 243-256 (The Geological Society, London, 1979).
10. Leake, B. E., Tanner, P. W. G. & Senior, A. *J. Petrol.* **16,** 237-277 (1975).
11. Slaughter, J., Kerrick, D. M. & Wall, V. J. *Am. J. Sci.* **275,** 143-162 (1975).
12. Elias, E. M., Macintyre, R. M. & Leake, B. E. *J. geol. Soc. Lond.* **145,** 649-660 (1988).
13. Barber, J. P. thesis, Univ. East Anglia (1985).
14. Rumble, D. *Rev. Miner.* **10,** 327-353 (1982).
15. Walther, J. V. & Helgeson, H. C. *Am. J. Sci.* **277,** 1315-1351 (1977).
16. Yardley, B. W. D. *J. geol. Soc. Lond.* **132,** 521-542 (1976).
17. Bowers, T. S., Jackson, K. J. & Helgeson, H. C. *Equilibrium Activity Diagrams* (Springer, New York, 1984).
18. Rumble, D., Ferry, J. M., Hoering, T. C. & Boucot, A. J. *Am. J. Sci.* **282,** 886-919 (1982).
19. Yardley, B. W. D. & Lloyd, G. E. *Geol. Mag.* **126,** 333-337 (1989).
20. Walther, J. V. & Hedgeson, H. C. *Am. J. Sci.* **280,** 575-606 (1980).
21. Moorbath, S., Bell, K., Leake, B. E. & McKerrow, W. S. in *Radiometric Dating for Geologists* (eds Hamilton, E. I. & Farquhar, R. M.) 259-298 (Wiley, London, 1968).

ACKNOWLEDGEMENTS. Stable isotope analyses were carried out at the British Geological Survey Isotope Geology Unit with the assistance of B. Spiro and P. Greenwood. We also thank G. Tanner for information about other skarn localities. This work was supported by NERC.

# A neurological dissociation between perceiving objects and grasping them

**M. A. Goodale, A. D. Milner*, L. S. Jakobson & D. P. Carey**

Department of Psychology, University of Western Ontario, London, Canada N6A 5C2
* Psychological Laboratory, University of St Andrews, St Andrews, Fife KY16 9JU, UK

**STUDIES of the visual capacity of neurological patients have provided evidence for a dissociation between the perceptual report of a visual stimulus and the ability to direct spatially accurate movements toward that stimulus. Some patients with damage to the parietal lobe, for example, are unable to reach accurately towards visual targets that they unequivocally report seeing[1,2]. Conversely, some patients with extensive damage to primary visual cortex can make accurate pointing movements or saccades toward a stimulus presented in their 'blind' scotoma[3-5]. But in investigations of visuomotor control in patients with visual disorders, little consideration has been given to complex acts such as manual prehension. Grasping a three-dimensional object requires knowledge not only of the object's spatial location, but also of its form, orientation and size. We have examined a patient with a profound disorder in the perception of such object qualities. Our quantitative analyses demonstrate strikingly accurate guidance of hand and finger movements directed at the very objects whose qualities she fails to perceive. These data suggest that the neural substrates for the visual perception of object qualities such as shape, orientation and size are distinct from those underlying the use of those qualities in the control of manual skills.**

The patient, D.F., is a 35-year-old woman who suffered irreversible brain damage following carbon monoxide intoxication. Magnetic resonance imaging revealed damage ventrally in the lateral occipital region (mainly areas 18 and 19), and in the parasagittal occipitoparietal region, but apparently sparing most of area 17 (ref. 6). There was also some indication of localized damage in the basal ganglia. Three to six months after her accident, neuropsychological and psychophysical testing revealed the presence of a profound 'visual form agnosia'[7,8]. D.F. showed poor perception of shape or orientation, whether this information was conveyed by colour, intensity, stereopsis,

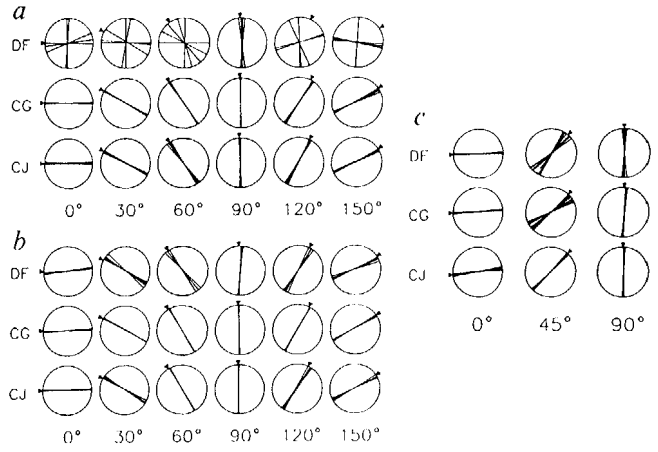


FIG. 1 The performance of the patient (D.F.) contrasted with that of two control subjects (C.G. and C.J.) of the same gender, age and handedness. Performance on each task was assessed through analysis of video records of each response. *a*, Polar plots indicate the orientation of a hand-held card which subjects were asked to match with the orientation of a slot (12.5 cm long, 3.8 cm wide, and 2 cm deep) in an upright disc, presented at a viewing distance of about 45 cm. The triangular mark on the circumference of each circle indicates the true orientation of the slot during the depicted trials. Although the patient's responses seemed to be somewhat more accurate when the slot was in the vertical (90°) orientation, each trial began with the card being held in the vertical position, which may have biased it to be the default orientation when D.F. was uncertain. *b*, Polar plots indicate the orientation of the card just before it made contact with the disc in the visually guided posting task. *c*, Polar plots indicate the orientation of a hand-held card when subjects were asked to position the card, with eyes closed, to match an imagined slot at 0°, 45° or 90°.

* To whom correspondence should be addressed.

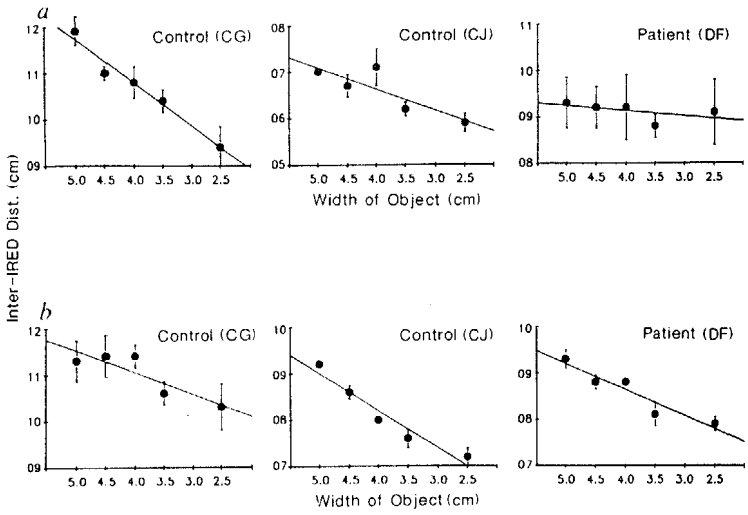


FIG. 2 In both the tasks described below, five white plaques (each with an overall area of 25 $cm^2$ on the top surface, but ranging in size from a 5 × 5 cm square to a rectangle measuring 2.5 × 10 cm) were presented, one at a time, at a viewing distance of approximately 45 cm. Infrared light-emitting diodes (IREDS) were attached to the tips of the index finger and thumb of the right hand. The position of each IRED was recorded by two infrared-sensitive cameras and stored on a WATSMART computer (Northern Digital Inc., Waterloo, Canada); the three-dimensional coordinates of the finger and thumb trajectories during a grasping movement and the changing distance between them were later reconstructed off-line at 100 Hz. *a*, The first task was to indicate manually the front-to-back extent of each object over a series of randomly ordered trials (means and s.e. values indicated for each object). In the patient (D.F.), unlike the controls (C.G. and C.J.), the aperture between the finger and thumb was not systematically related to the width of the target objects when performing this task ($r(19) = +0.10$ (n.s.), versus $r(19) = +0.82$ ($P < 0.01$) and $r(19) = +0.65$ ($P < 0.01$)). In interpreting these graphs it is the slope of the function that is important rather than the absolute values plotted, as the placement of the IREDs and the size of the hand and fingers varied somewhat from subject to subject. *b*, In the second task, subjects were asked to reach out and pick up each target object, again over a series of trials. In this case, the maximum aperture between the index finger and thumb, which was achieved well before contact with the object, was systematically related to the width of the objects in both the patient ($r(19) = +0.81$ ($P < 0.01$)) and the control subjects ($r(18) = +0.65$ ($P < 0.01$) and $r(19) = +0.91$ ($P < 0.01$)). The trial-to-trial variance in D.F.'s performance was far greater on the perceptual matching task (*a*) than it was on the grasping task (*b*).

motion, proximity, continuity or similarity. Extensive visual testing indicated that the patient's visual form agnosia could not be reduced to a simple sensory deficit.

At the time of our testing, 15 months after the accident, D.F.'s verbal IQ was above average but the visual form agnosia[7,8] persisted. Also still present was a striking dissociation between the patient's ability to perceive object orientation and her ability to direct accurate reaching movements toward objects in different orientations[8]. We tested her orientation perception in several ways: to choose which of four line orientations depicted on a card matched the orientation of a large slot in an upright disk; to turn a hand-held card until its orientation matched that of the slot; and to indicate verbally the orientation of an oblong block placed on the table in front of her. Despite the variety of response options, D.F.'s performance on all these perceptual tasks was grossly impaired: her responses were highly variable and included gross errors such as judging horizontal to be vertical (see Fig. 1*a*).

In sharp contrast to her performance on these perceptual tasks, when the patient was asked to reach out and 'post' the hand-held card through the slotted disc described above, her performance was excellent (see Fig. 1*b*). Indeed, analysis of video records of each reaching movement revealed that, like the controls, D.F. began to orient the card correctly even as her hand was being raised from the start position in this task. Similarly, when asked to pick up a block placed at different orientations on the table surface in front of her, she oriented her hand appropriately very early in the reaching movement and grasped the object normally.

D.F.'s difficulty is not one of comprehension. When asked to imagine a slot at different orientations with her eyes closed, she could rotate the hand-held card to the imagined orientation just as accurately as the two age-matched controls (see Fig. 1*c*). Thus, her difficulty seems to be in using visual orientation information for perceptual or cognitive purposes, even though such information is accurately used in visuomotor action. The opposite dissociation has been described in patients with optic ataxia, who can perceive orientation well but are poor at moving their hand into an oriented slot[2].

The persistence of this remarkable dissociation led us to investigate whether other aspects of object form, such as size, could modulate D.F.'s grasping responses. Accordingly we constructed five pairs of white plaques of equal area but different dimensions, ranging from a square to an elongated rectangle[9]. As an initial perceptual test, the objects were presented as pairs in all possible combinations, and D.F. was asked to indicate whether the objects were alike or different. Whereas normal subjects had no difficulty discriminating any of the stimuli on this task, the patient scored no better than chance (52%). In a task of perceptual matching, D.F. and the two control subjects were asked to indicate with the index finger and thumb of their right hands the front-to-back extent (the width) of plaques placed one at a time on the table in front of them. Unlike the two control subjects, D.F.'s estimates did not change as a function of the width of the plaques (Fig. 2*a*). Thus, in both her verbal and her manual responses there was no evidence that the patient was sensitive to differences in the dimensions of the stimuli.

When we asked D.F. to reach out and pick up the plaques the results were quite different. Now, the aperture between her index finger and thumb was systematically related to the width of the object (see Fig. 2*b*), a relationship reliably observed in studies of normal prehension[10]. In fact, her performance was indistinguishable from that of our controls. (To confirm that she understood the perceptual matching task, we asked D.F. to indicate the width of an imagined plaque with her finger and thumb. She now showed accurate scaling with a correlation of +0.78 between grip size and imagined width.)

Our data show that a person with brain damage may retain the ability to calibrate normal aiming and prehension movements with respect to the orientation and dimensions of objects, despite a profound inability to report, either verbally or manually, these same visual properties. This dissociation suggests that at some level in normal brains the visual processing underlying 'conscious' perceptual judgements must operate separately from that underlying the 'automatic' visuomotor guidance of skilled actions of the hand and limb. Note that this inferred separation does not correspond to the two streams of output from primary visual cortex generally identified in the primate brain—a ventral one for object identification and a dorsal one for spatial localization[11,12]. Our observations indicate separate processing systems not for different subsets of visual information, but for the different uses to which vision can be put. If correct, our reasoning suggests that in trying to understand the functions of the many different visual areas in primate cortex (as well as subcortical visual pathways) it may be

important to examine the pattern of their output connections, in addition to their visual inputs and processing characteristics. □

Received 17 August; accepted 22 October 1990.

1. Damasio, A. R. & Benton, A. L. *Neurology* **29,** 170–178 (1979).
2. Perenin, M.-T. & Vighetto, A. *Brain* **111,** 643–674 (1988).
3. Perenin, M.-T. & Jeannerod, M. *Neuropsychologia* **4,** 1–7 (1975).
4. Weiskrantz, L., Warrington, E. K., Sanders, M. D. & Marshall, J. *Brain* **97,** 709–728 (1974).
5. Poeppel, E., Held, R. & Frost, D. *Nature* **243,** 295–296 (1973).
6. Damasio, H. & Damasio, A. R. *Lesion Analysis in Neuropsychology* (Oxford University Press, New York, 1989).
7. Milner, A. D. & Heywood, C. A. *Cortex* **25,** 489–494 (1989).
8. Milner, A. D. *et al. Brain* (in the press).
9. Efron, R. *Boston Studies in the Philosophy of Science* **4,** 137–173 (1969).
10. Jeannerod, M. In *Attention and Performance IX* (eds J. Long & A. Baddeley) 153–168 (Erlbaum, Hillsdale, New Jersey, 1981).
11. Ungerleider, L. G. & Mishkin, M. In *Analysis of Visual Behavior* (eds D. J. Ingle, M. A. Goodale & R. J. W. Mansfield) 549–580 (MIT, Cambridge, 1982).
12. Maunsell, J. H. R. & Newsome, W. T. *A. Rev. Neurosci.* **10,** 363–401 (1987).

ACKNOWLEDGEMENTS. Supported by grants from the Medical Research Council of Canada to M.A.G. and the William Ramsay Henderson Trust to A.D.M.; D.P.C. and L.S.J. hold MRCC studentships.

# Long-term potentiation of NMDA receptor-mediated synaptic transmission in the hippocampus

**Zafar I. Bashir*, Simon Alford*, Stephen N. Davies*†, Andrew D. Randall‡§ & Graham L. Collingridge*§‖**

Departments of * Pharmacology and ‡ Biochemistry, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, UK and § Department of Pharmacology, The Medical School, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

**NEUROTRANSMISSION at most excitatory synapses in the brain operates through two types of glutamate receptor termed α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors; these mediate the fast and slow components of excitatory postsynaptic potentials respectively[1–3]. Activation of NMDA receptors can also lead to a long-lasting modification in synaptic efficiency at glutamatergic synapses; this is exemplified in the CA1 region of the hippocampus, where NMDA receptors mediate the induction of long-term potentiation (LTP)[4]. It is believed that in this region LTP is maintained by a specific increase in the AMPA receptor-mediated component of synaptic transmission[5,6]. We now report, however, that a pharmacologically isolated NMDA receptor-mediated synaptic response can undergo robust, synapse-specific LTP. This finding has implications for neuropathologies such as epilepsy and neurodegeneration, in which excessive NMDA receptor activation has been implicated[7]. It adds fundamentally to theories of synaptic plasticity because NMDA receptor activation may, in addition to causing increased synaptic efficiency, directly alter the plasticity of synapses.**

Synaptic responses evoked in area CA1 comprise an excitatory postsynaptic potential (e.p.s.p.), that is mediated by AMPA and NMDA receptors, and an inhibitory postsynaptic potential (i.p.s.p.), the first phase of which is mediated by $GABA_A$ receptors. To investigate whether the NMDA receptor-mediated component of the synaptic response is able to undergo LTP, we blocked the AMPA receptor-mediated component with 10 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and the $GABA_A$ receptor-mediated component with 50 μM picrotoxin. Two separate inputs were stimulated alternately (each at 0.033 Hz) so as to evoke small (0.4–0.9 mV) NMDA receptor-mediated field e.p.s.ps. After obtaining a stable baseline for about 15 min, a period of high-frequency (tetanic) stimulation was delivered (20–25 shocks at 100 Hz, test intensity) and responses were then followed for at least a further 45 min. In 6 out of 8 slices examined in this way, synapse-specific LTP (defined as at least a 20% increase in amplitude 45 min after the tetanus) was obtained (Fig. 1*a*, *b*). To ensure that the potentiated responses were mediated entirely through NMDA receptors, the specific NMDA receptor antagonist D-2-amino-5-phosphonopentanoate (AP5; 20 μM) was applied; this reversibly blocked the response on each occasion ($n = 3$; Fig. 1*b*). We next investigated whether LTP of NMDA receptor-mediated responses required NMDA-receptor activation during the tetanus. We first delivered a tetanus in the presence of 50 μM AP5, a concentration of antagonist that blocks induction of conventional LTP, and then, after washout of AP5, applied a second identical tetanus to the same input. As shown in Fig. 1*c*, AP5 reversibly blocked the induction of LTP of the NMDA receptor-mediated response ($n = 3$).

Following the induction of LTP, the largest change in the synaptic waveform occurred several tens of milliseconds after the stimulus and was manifest as a burst of population spikes (Fig. 1*a*). From about 30 ms after the stimulus, a $GABA_B$ receptor-mediated i.p.s.p.[8] is coincident with the NMDA receptor-mediated synaptic component. The potentiation might therefore result, in part, from a long-lasting depression of $GABA_B$ receptor-mediated synaptic inhibition, rather than a direct potentiation of the NMDA receptor-mediated response. To preclude possible alterations in the $GABA_B$ receptor-mediated i.p.s.p., we applied the $GABA_B$ receptor antagonist 2-hydroxysaclofen (500 μM). Under these conditions, in 5 out of 7 slices, tetanic stimulation resulted in LTP like that induced in the absence of 2-hydroxysaclofen.

The most pronounced change following tetanization is in the ability of the response to elicit spike firing, reflected in the appearance of asynchronous population spikes (Fig. 1*a*). This is reminiscent of so-called E–S potentiation (e.p.s.p. to spike coupling) and could conceivably be due to modification of voltage-dependent conductances that are evoked by the NMDA receptor-mediated e.p.s.p., rather than a direct alteration in the NMDA receptor-mediated conductance *per se*. In the next series of experiments we investigated whether LTP of the NMDA receptor-mediated synaptic current occurred, using the perforated patch method of whole-cell recording from brain slices[9]; this provides a high-resolution voltage-clamp of the NMDA receptor-mediated response[10,11] without the problem of intracellular dialysis, which reduces the likelihood of inducing LTP with time[12]. Using this method, in the presence of CNQX and picrotoxin, we obtained LTP in each of 7 cells tested (Fig. 2). The mean amplitude of NMDA receptor-mediated synaptic currents, recorded at a membrane potential of −70 mV, 30 min following the tetanus, was 143 ± 13% of control ($P < 0.01$). In addition, we obtained similar LTP in each of two cells tetanized in two slices treated additonally with the $GABA_B$ antagonist CGP 35348 (500 μM; Fig. 3). The potentiated synaptic current was blocked by AP5 ($n = 2$) and increased in amplitude with membrane depolarization ($n = 2$), confirming that it represented an NMDA receptor-mediated synaptic current in the postsynaptic cell (Fig. 3).

Our data demonstrate that NMDA receptor-mediated synaptic transmission is able to undergo a long-lasting modification. Previous reports have failed to observe significant potentiation of the isolated NMDA receptor-mediated synaptic response[5,6], possibly because it is more difficult to induce LTP of the isolated NMDA receptor-mediated component (compared with conventional LTP). A possible reason for this is that low-frequency activation of the NMDA receptor system, which is minimized under physiological conditions by synaptic inhibition[3,13], can reduce the probability of inducing LTP[14]. For this reason we used a stimulus intensity that evoked small NMDA receptor-mediated e.p.s.ps and performed the voltage-clamp experiments

† Present address: Division of Physiology, School of Biomedical Sciences, Marischal College, Aberdeen AB9 1AS, UK.
‖ To whom correspondence should be addressed at the University of Birmingham.