histories of regular and spontaneous ovulation. They were the first women who met our subject criteria among those responding to our request for volunteers and none dropped out once the experiment had begun. We collected compounds from the axillae of 9 donor women in hormonally distinct phases of the menstrual cycle and applied them daily just under the noses of 20 recipients. All participants were unaware of the experiment's hypothesis and the source of the compounds. The study was presented as focused primarily on the development of non-invasive methods for detecting ovulation, and secondarily on sensitivity to the odour of small amounts of 'natural essences' (consent was obtained for a list of 30 compounds).

Axillary compounds. As in other species, human pheromones might be produced by apocrine glands (active only during reproductive maturity), eccrine glands (which produce sweat that contains compounds found also in saliva and urine), exfoliated epithelial cells or bacterial action[22–24]. We collected compounds from axillae because they contain all four of these potential sources and because the two previous, albeit highly criticized, attempts to study this issue used axillary compounds[3,4,25–28]. The 9 donors bathed without perfumed products every day and then wore 4×4 cotton pads in their axillae for at least eight hours. Each pad was cut into four sections for distribution to different recipients, treated with 4 drops of 70% isopropyl alcohol[25] and then frozen immediately at −80 °C in a glass vial.

Menstrual cycle assessment. Donors provided urine samples every evening, which we assayed for LH to detect the onset of the LH surge that triggers ovulation[29]. This singular hormonal event unambiguously demarcates the follicular from the ovulatory phases of the cycle. The LH surge was used together with data on vaginal secretions, menses, basal body temperature, and a rise in progesterone glucuronide in the postovulatory luteal phase, to classify each pad as containing compounds produced during the follicular phase (2 to 4 days before the onset of the LH surge) or the ovulatory phase (the day of the LH surge onset and the 2 subsequent days). To ensure a similar stimulus for all recipients regardless of individual differences among donors, all 9 donors contributed equally to the follicular and ovulatory compounds received by each subject.

As it is not yet known when during the menstrual cycle women are physiologically most sensitive to putative pheromones, applying compounds every day ensured covering a potentially sensitive period. However, our computer simulation experiments indicated that in rats this pheromonal-sensitive period occurs mid-cycle, around the time of ovulation[8] (a period when women are particularly sensitive to some olfactory stimuli[30]). Any condition preventing exposure to the compounds, such as nasal congestion anytime during the mid-cycle period from three days before to two days after the preovulatory LH, could weaken the effect. We analysed the data taking this into account.

Experimental design. All recipients were studied for one baseline cycle without exposure to axillary compounds. Then, in a crossover experimental design during the next four consecutive cycles, axillary compounds were applied daily by wiping a thawed pad above the recipients upper lip. Half of the recipients ($n = 10$) received follicular compounds daily for two menstrual cycles and were then switched to exposure to ovulatory compounds for the next two cycles. The other 10 recipients received the same compounds in the reverse order. After applying the compounds, recipients were free to go about their normal activities but were asked not to wash their faces for the next six hours. All but two subjects, who missed only the last cycle of their second treatment, completed all five cycles of the experiment.

A between-subjects control group was provided by women (the donors) who collected all ovarian-cycle measures, but received only the carrier above their upper lip each day: 70% isopropyl alcohol. In addition, because the two-day change in menstrual cycle length (expected from the initial study[2]) is substantially less than individual variation in cycle length typical for this age group[10], we created within-subjects controls by measuring the effect on the menstrual cycle in terms of a change in length from each individual subject's cycle preceding each condition. (For experimental subjects this was the cycle that preceded exposure to each type of compound; for control subjects this was the cycle that preceded exposure to the carrier, 70% alcohol).

Received 3 October; accepted 8 January 1998

1. Beauchamp, G. K., Doty, R. L., Moulton, D. G. & Mugford, R. A. In *Mammalian Olfaction, Reproductive Processes and Behavior* (ed. Doty, R. L.) 144–157 (Academic, New York, 1976).
2. McClintock, M. K. Menstrual synchrony and suppression. *Nature* **291,** 244–245 (1971).
3. Graham, C. A. Menstrual synchrony: an update and review. *Human Nature* **2,** 293–311 (1992).
4. Weller, L. & Weller, A. Human menstrual synchrony: A critical assessment. *Neurosci. Behav. Rev.* **17,** 427–439 (1993).
5. Weller, A. & Weller, L. Menstrual synchrony under optimal conditions: Bedouin families. *J. Comp. Psychol.* **111,** 143–151 (1997).
6. McClintock, M. K. Estrous synchrony: Modulation of ovarian cycle length by female pheromones. *Physiol. Behav.* **32,** 701–705 (1984).
7. McClintock, M. K. *Pheromones and Reproduction in Mammals* (ed. Vandenbergh, J. G.) 113–149 (Academic, New York, 1983).
8. Schank, J. & McClintock, M. K. A coupled-oscillator model of ovarian-cycle synchrony among female rats. *J. Theor. Biol.* **157,** 317–362 (1992).
9. Christian, M. S., Galbraith, W. M., Voytek, P. & Mehlman, M. A. *Advances in Modern Environmental Toxicology III: Assessment of Reproductive and Teratogenic Hazards* (Princeton Scientific, NJ, 1983).
10. Treoloar, N. E., Boynton, R. E., Gorghild, G. B. & Brown, B. W. Variation of the human menstrual cycle through reproductive life. *Int. J. Fertil.* **12,** 77–126 (1967).
11. Cutler, W. B., Garcia, C. R., Kreiger, A. M. Luteal phase defects: A possible relationship between short hyperthermic phase and sporadic sexual behavior in women. *Horm. Behav.* **13,** 214–218 (1979).
12. Ryan, K. D. & Schwartz, N. B. Grouped female mice: demonstration of pseudopregnancy. *Biol. Reprod.* **17,** 578–583 (1977).
13. McClintock, M. K. Social control of the ovarian cycle and the function of estrous synchrony. *Am. Zool.* **21,** 243–256 (1981).
14. Mennella, J., Blumberg, M., Moltz, H. & McClintock, M. K. Inter-litter competition and communal nursing among Norway rats: Advantages of birth synchrony. *Behav. Ecol. Sociobiol.* **27,** 183–190 (1990).
15. LeFevre, J. L. & McClintock, M. K. Isolation accelerates reproductive senescence and alters its predictors in female rats. *Horm. Behav.* **25,** 258–272 (1991).
16. Vandenbergh, J. G.(ed.). *Pheromones and Reproduction in Mammals* (Academic, New York, 1983).
17. Rasmussen, L. E. L., Perris, T. E. & Gunawardena, R. Isolation of potential musth-alerting signals from the temporal gland secretions of male Asian elephants (*Elephas maximus*): A new method. *Chemical Senses* **19,** 540 (1994).
18. Leon, M. & Moltz, H. The development of the pheromonal bond in the albino rat. *Physiol. Behav.* **8,** 683–686 (1972).
19. Galef, G. Social identification of toxic diets by Norway rats (*Rattus norvegicus*). *J. Comp. Psychol.* **100,** 331–334 (1986).
20. Johnson, E. Pheromones, the vomeronasal system and communication: From hormonal responses to individual recognition. *Ann. N.Y. Acad. Sci.* (in the press).
21. Rottman, S. J. & Snowdon, C. T. Demonstration and analysis of an alarm pheromone in mice. *J. Comp. Physiol. Psychol.* **81,** 483–490 (1972).
22. Nixon, A., Mallet, A. I. & Gower, D. B. Simultaneous quantification of five odorous steroids (16-androstenes) in the axillary hair of men. *J. Ster. Biochem.* **29,** 505–510 (1988).
23. Cohn, B. A. In search of human skin pheromones. *Arch. Dermatol.* **130,** 1048–1051 (1994).
24. Spielman, A. I., Zeng, X. N., Leyden, J. J. & Preti, G. Proteinaceous precursors of human axillary odor: isolation of two novel odor-binding proteins. *Experimentia* **51,** 40–47 (1995).
25. Russell, M. J., Switz, G. M., Thompson, K. Olfactory influences on the human menstrual cycle. *Pharmacol. Biochem. Behav.* **13,** 737–738 (1980).
26. Preti, G., Cutler, W. B., Garcia, C. R., Huggins, G. R. & Lawkey, H. J. Human axillary secretions influence women's menstrual cycles: The role of donor extract from females. *Horm. Behav.* **20,** 474–482 (1986).
27. Doty, R. Olfactory communication in humans. *Chem. Senses* **6,** 351–376 (1981).
28. Wilson, H. C. Female axillary secretions influence women's menstrual cycles: A critique. *Horm. Behav.* **21,** 536–546 (1987).
29. Stern, K. & McClintock, M. K. In *Psychopharmacology of Women* (eds Jensvold, M. F., Halbreich, U. & Hamilton, J.) 393–413 (Am. Psychiatry Press, Washington DC, 1996).
30. Doty, R. L., Snyder, P. J., Huggins, G. R. & Lowry, L. D. Endocrine, cardiovascular and psychological correlates of olfactory sensitivity changes during the human menstrual cycle. *J. Comp. Physiol. Psychol.* **95,** 45–60 (1981).

Acknowledgements. We thank T. Z. Snyder for editing and J. Altmann, J. Charrow, S. Fisher and S. Goldin-Meadow for their comments. This work was supported by the US NIMH and NIH and a grant from the John D. and Catherine T. MacArthur Foundation.

Correspondence and requests for materials should be addressed to M.K.M. (e-mail: mkm1@midway.uchicago.edu).

Motor role of human inferior parietal lobe revealed in unilateral neglect patients

Jason B. Mattingley*, Masud Husain†, Chris Rorden‡, Christopher Kennard† & Jon Driver‡

* *Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, UK*
† *Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK*
‡ *Institute of Cognitive Neuroscience, Department of Psychology, University College London, Gower Street, London WC1E 6BT, UK*

The exact role of the parietal lobe in spatial cognition is controversial. One influential hypothesis proposes that it subserves spatial perception[1], whereas other accounts suggest that its primary role is to direct spatial movement[2,3]. For humans, it has been suggested that these functions may be divided between inferior and superior parietal lobes, respectively[2,4]. In apparent support of

a purely perceptual function for the inferior parietal lobe (IPL), patients with lesions to this structure, particularly in the right hemisphere, exhibit unilateral spatial neglect (deficient awareness for the side of space opposite to that of their lesion)[5]. Here we show that patients with right IPL lesions also have a specific difficulty in initiating leftward movements towards visual targets on the left side of space. This motor impairment was not found in neglect patients with frontal lesions, contrary to previous proposals that motor aspects of neglect are particularly associated with anterior damage[6–9]. Our results suggest that the human IPL operates as a sensorimotor interface, rather than subserving only perceptual functions.

Unilateral neglect patients often fail to acknowledge stimuli located contralateral to their lesion, or are slow to respond to them, despite relatively preserved afferent inputs on the affected side[5]. Although neglect clearly has a perceptual component[10–13], it may also involve a directional bias in motor control, which disadvantages movements toward contralesional stimuli[6–9,14]. Previous evidence for motor deficits in neglect has come mainly from patients with large lesions involving the frontal lobe[7–9], rather than damage restricted to just the IPL, and from tasks which sought to isolate motor components of neglect by having patients make unnatural movements away from visual targets[7,8]. One problem with such tasks is that patients with frontal lobe lesions may perform abnormally because of their general difficulties with highly incompatible responses[15,16].

Our study introduces a new method which allows separation of sensory and motor components of neglect, without ever requiring movements away from targets. Rather than applying this test to patients with large lesions extending across both the parietal and frontal lobes, we studied two separate groups with focal lesions. The lesions of the posterior group were centred on the right IPL, allowing a critical test of whether this structure is purely perceptual. The anterior group had focal lesions centred on the right inferior frontal lobe (IFL). Damage here can also produce neglect[17,18], but no study has contrasted IFL with IPL lesion patients to test whether motor aspects of neglect depend on anterior damage.

In our reaching task, sensory information about target location remained constant while the direction of movement required to reach towards the target was manipulated. Visual fixation was maintained at a central position while the start position of the responding hand was varied. Visual targets could appear on the left or right of fixation. Patients made fast reaches with their right hand towards whichever light turned green. In separate blocks of trials the right hand started: midway between the potential targets (at the body midline); to the extreme left of both targets; or to the extreme right (Fig. 1a–c).

In left neglect patients, reaction times to a left target should be slower than those to a right target when the hand starts centrally (Fig. 1a). This left delay could be due to impaired perceptual attention for left targets, or to a problem in initiating leftward movements, or to some combination of these deficits. The critical situation for evaluating any directional motor impairment arose when the hand started from an extreme left position (Fig. 1b). In this case, a rightward movement was now required to reach towards a target on the left of fixation. If delayed reactions to left targets from a central start were caused by a problem in initiating leftward movements, then this delay should be reduced when only rightward movements were required, from the left start. We also examined reaches with an extreme right start, from which all movements were leftward (Fig. 1c).

Six patients with left neglect after right-hemisphere stroke were tested, at a mean of 49 days post stroke. Lesion reconstructions[19] are shown in Fig. 2. The region of cortical lesion overlap for the three patients with posterior strokes was in the IPL (Fig. 2c); none of their

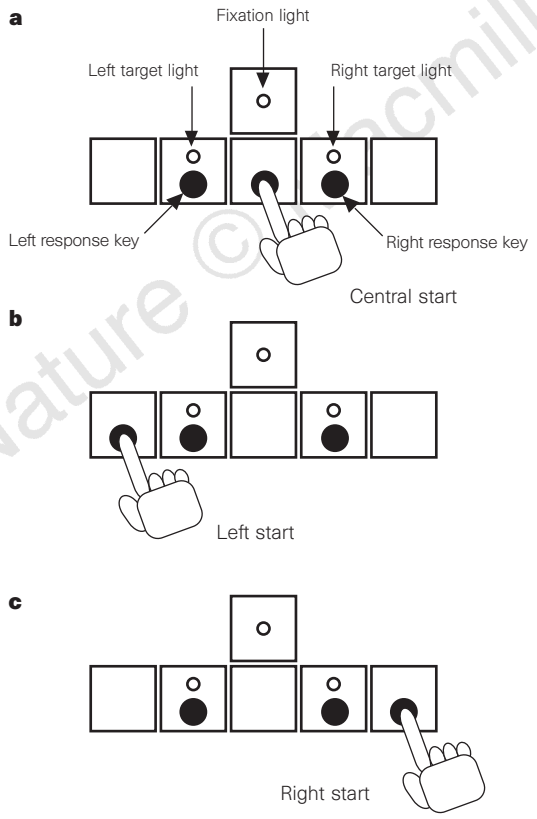

Figure 1 Reaction times to left or right visual targets were measured in a reaching task (experiment 1) and a no-reach task (experiment 2) using the same apparatus. In both conditions, the hand was positioned, in separate blocks of trials, either at a central (**a**), extreme left (**b**), or extreme right (**c**) start position. In the reaching task, subjects had to move their hand from the start position to press the key immediately beneath the green target. In the no-reach task, their response was to depress the start key on detecting a green target, and so no spatial reach was required.

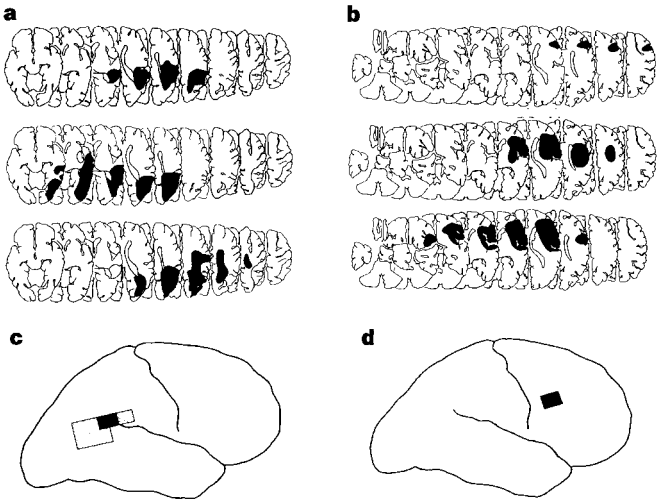

Figure 2 Extent of right-hemisphere lesions in neglect patients. **a**, Posterior or **b**, anterior strokes, plotted from CT scans on to axial templates[19]. Lateral views of the brain, demonstrating the common cortical (solid) and subcortical (hatched) lesion, are shown in (**c**) and in (**d**) for patients with posterior or anterior lesions, respectively. The common cortical area in the posterior group occupies a small region of the right inferior parietal lobe (IPL); for the anterior group, it occupies a small region of the right inferior frontal lobe (IFL). Note that for patients with anterior lesions, the common subcortical zone lies immediately beneath the common cortical zone.

lesions involved the superior parietal cortex. The region of cortical lesion overlap for the three anterior patients was in the IFL (Fig. 2d). All six subjects showed left neglect on standard clinical tests. On the Mesulam shape-cancellation task[20] the IPL patients found a mean of only 33/60 targets, all on the right of the sheet. The IFL patients found a mean of 34/60 targets (all on the right), showing comparable severity of clinical neglect. No patient had optic ataxia or apraxia.

Mean reaction times to initiate a reach for left versus right targets from each start position are shown in Fig. 3, separately for IPL and IFL groups. IPL patients showed substantially slower reaction times for left targets than right targets when the hand started centrally, indicating left neglect. In the critical condition where the hand started from the extreme left (so that left targets now required a rightward movement), the disadvantage for left targets was dramatically reduced. This pattern was found for all three IPL patients, and suggests that a substantial component of their difficulty with left targets from a central start was due to a motor deficit in initiating leftward reaches, rather than solely to a perceptual deficit in detecting left targets.

When the hand started from the extreme right, reaction times for IPL patients were as for a central start; reaches were still initiated more slowly for left than right targets, even though both required leftward movements. The motor impairment in the IPL patients is therefore not simply a difficulty in initiating any leftward movement; rather it is a specific difficulty in initiating leftward movements to targets located in the left visual field. Thus, both sensory and motor factors determine the IPL patients' performance.

For the IFL group, hand start position had no significant effects on reaction time. All three IFL patients reacted more slowly to left than right targets (revealing neglect), but did so regardless of the direction of movement required. Because the IFL group did not show the motor initiation deficit identified in the IPL patients, they serve as a control group to show that the IPL pattern is lesion-specific. We have also confirmed that a further control group of normal elderly people do not show the IPL pattern.

The IPL pattern could perhaps be attributed to the sensory attention of those patients being 'cued' towards their neglected left side, by proprioceptive and/or visual inputs from the responding hand when it rested on the left start key. Experiment 2 tested this alternative to our motor account, using a 'no-reach' control task. We varied hand position as before, but now the patients were only required to press the start key as soon as they detected a green target on either side. Thus, they responded where their hand was already located, rather than reaching towards the target. Central fixation was again required, so the visual events were as in experiment 1. Likewise, the afferent inputs from the right hand were also exactly as before for the three different start positions. If the previous IPL pattern was due to these afferent inputs, the new task should replicate it. If instead the critical factor was the direction of reaching required for left targets, the results should change, because directional reaches were no longer required.

Mean results from the control no-reach task are shown in Fig. 4. Unlike the reaching task (compare left graphs in Fig. 4 versus Fig. 3), changing the start position of the hand now had no effect on the IPL group. Responses were still slower overall for left targets, revealing a perceptual component to these patients' neglect (delayed detection of left visual events); but critically, there was no longer an improvement for left targets when the hand was located on the left. This excludes any explanation for experiment 1 in terms of 'cueing' by afferent inputs from the right hand when at a left start. The effect of start position in experiment 1 for IPL patients must therefore have been due to the motor deficit we propose, impairing the initiation of leftward reaches to left targets.

The IFL group showed no effect of start position in either experiment. The absence of a motor initiation deficit for leftward reaches in these anterior patients (experiment 1) seems contrary to previous suggestions of a specific association between anterior lesions and motor components of neglect[6–9]. However, previous studies did not test patients with focal frontal lesions as here, but rather with larger lesions involving both parietal and frontal lobes.

The specific motor initiation deficit found in the IPL patients has parallels with recent electrophysiological findings from monkey posterior parietal cortex. Cells there were previously thought to have primarily sensory or attentional roles[21,22], but a recent study observed neuronal discharges tuned not only for a sensory location, but also for the movement (a saccade or reach) being planned towards it[3]. Human parietal cortex may contain neurons with similar response properties, computing discrepancies between current hand position and target location[23–25]. An impairment to such

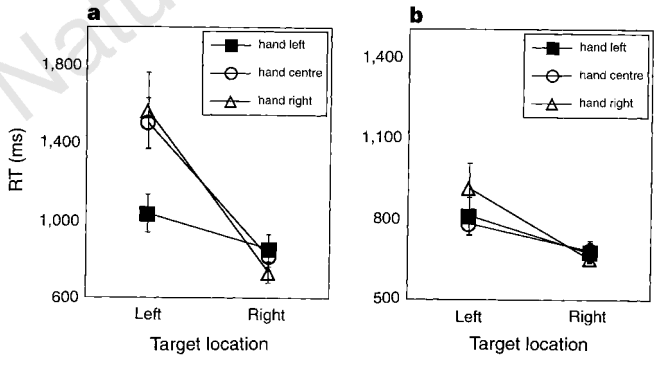

Figure 3 Mean reaction time (RT) to initiate movements towards left versus right targets, from three different start positions in the reaching task of experiment 1. **a**, IPL patients; **b**, IFL patients. With a central start, RT to left targets was slower than for right targets, consistent with left neglect ($P < 0.05$ for five patients; $P < 0.06$ for one frontal patient). For the IPL group, slower RT for left than right targets was found from the central and right start positions ($F(1) = 27.72, P < 0.01$ and $F(1) = 40.36$, $P < 0.01$, respectively), but critically not from the left start position ($F(1) = 1.92$, NS). In contrast, for the IFL group there was no effect of start position on RT to left versus right targets ($F(2, 4) = 2.91$, NS). Direct comparison of the two groups confirmed that the RT difference between left and right targets depended on start position for IPL patients but not IFL patients ($F(2, 4) = 8.18$, $P < 0.5$).

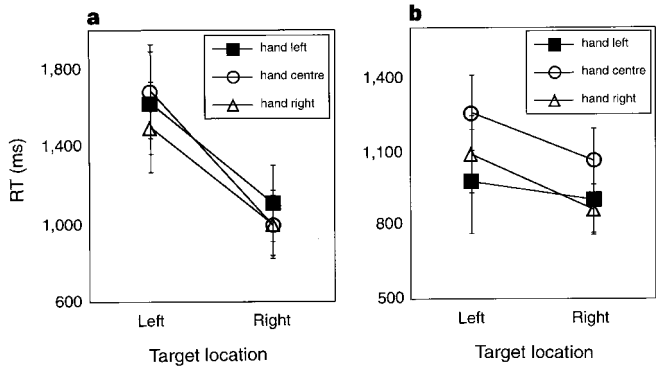

Figure 4 Mean RT to detect left versus right targets, for the three different hand positions in the no-reach task of experiment 2. **a**, IPL patients; RT was significantly longer for left than right targets, but this was unaffected by hand position ($F(2, 4) = 2.78$, NS). Unlike the reaching task of experiment 1 (compare with Fig. 3a), there was no improvement in RT to the left target when the hand was placed on the extreme left. **b**, IFL patients: RT to left versus right targets was again unaffected by hand start position ($F(2, 4) = 4.58$, NS).

parietal computations after right IPL damage might be responsible for the observed delay in initiating leftward movements to targets in the left hemispace. The parietal lobe is increasingly regarded as the final stage of a 'dorsal stream' of visual pathways (as distinct from a 'ventral' stream to the temporal lobe)[1]. Milner and Goodale[2,4] proposed that the dorsal stream directs spatial movements, consistent with the misreaching seen in patients with superior parietal lesions[26]. But before this study, there was no evidence for motoric impairments after inferior parietal damage. Indeed, Milner and Goodale considered human IPL primarily as part of the ventral stream concerned with perceptual awareness, although they suggested it may 'co-opt' dorsal processes[2]. Our results show for the first time that patients with right IPL lesions have an 'intentional' impairment in initiating leftward movements towards targets in the left hemispace, in addition to their perceptual difficulties. We therefore conclude that the human IPL acts as a sensorimotor interface, rather than having exclusively perceptual or motor functions. □

Methods

The apparatus comprised six white plastic boxes (each 10 cm square, 4.5 cm high) mounted on a board (Fig. 1). One box was placed centrally, further away from the patient than the remaining five, with a yellow light-emitting diode (LED) in it serving as the fixation point. Three boxes each had a microswitch connected to a response key (diameter 32 mm). Two of these boxes also contained bi-colour (green/red) LEDs which served as target (green) or distractor (red) stimuli (roughly 8° eccentricity from fixation). The response key in the third box served as the start key. This start box could be moved to occupy the central, extreme left or extreme right position (Fig. 1a–c). The remaining two boxes filled spaces unoccupied by boxes with response keys. A computer controlled the LEDs and recorded key-presses.

The patients sat with body midline aligned with the central fixation point. Eye position was monitored by an investigator, and trials with saccades before limb movement were discarded. The patients responded with the index finger of their right hand. They received at least 15 practice trials on both the reaching and no-reach tasks, being randomly assigned to start on either task. Each block of 50 experimental trials comprised a random sequence of 20 target-only trials with just a green LED illuminated (10 left; 10 right); 20 target-plus-distractor trials, with green target on one side and concurrent red distractor on the other side (10 left targets; 10 right); and 10 distractor-only ('catch') trials, with only a red distractor (5 left catch; 5 right). Response had to be withheld on catch trials. Data presented are pooled over target-only and target-plus-distractor trials, as preliminary analyses found no difference. Start position was blocked, in a randomized order across subjects.

In the reaching task of experiment 1, trials began with the onset of the yellow central fixation LED, as a signal to depress the start key. A variable 500–1,000 ms after this key was depressed, the fixation LED extinguished, and a target (green LED), a distractor (red LED), or a target on one side plus a distractor on the opposite side, were illuminated. Patients reached as quickly as possible to press the key immediately beneath the green LED. They were asked to ignore any red LED, and to withhold movements on catch trials. Reaction time to initiate the movement was recorded. On each trial, target and distractor LEDs remained illuminated until a key was pressed, or for a maximum of 4,000 ms. The 'no-reach' task used the same apparatus, but patients were instructed to depress and then gently release the start key when the fixation LED came on. When they saw a target (green LED) they had to depress the start key (on which their finger was still resting) as fast as possible. Reaching and no-reach tasks were intermingled within each session to allow a meaningful comparison.

Received 1 October; accepted 20 November 1997.

1. Ungerleider, L. G. & Mishkin, M. in *Analysis of Visual Behaviour* (eds Ingle, D. J., Goodale, M. A. & Mansfield, R. J. W.) 549–586 (MIT Press, Cambridge, MA, 1982).
2. Milner, A. D. & Goodale, M. A. *The Visual Brain in Action* (Oxford Univ. Press, Oxford, 1995).
3. Snyder, L. H., Batista, A. P. & Andersen, R. A. Coding of intention in the posterior parietal cortex. *Nature* **386,** 167–170 (1997).
4. Milner, A. D. in *Parietal Lobe Contributions to Orientation in 3D Space* (eds Thier, P. & Karnath, H.-O.) 3–22 (Springer, Heidelberg, 1997).
5. Robertson, I. H. & Marshall, J. C. (eds) *Unilateral Neglect: Clinical and Experimental Studies* (Lawrence Erlbaum, Hillsdale, 1993).
6. Mesulam, M-M. A cortical network for directed attention and unilateral neglect. *Ann. Neurol.* **10,** 309–325 (1981).
7. Bisiach, E., Geminiani, G., Berti, A. & Rusconi, M. Perceptual and premotor factors of unilateral neglect. *Neurology* **40,** 1278–1281 (1990).
8. Tegnér, R. & Levander, M. Through a looking glass. A new technique to demonstrate directional hypokinesia in unilateral neglect. *Brain* **114,** 1943–1951 (1991).
9. Mattingley, J. B., Bradshaw, J. L. & Phillips, J. G. Impairments of movement initiation and execution in unilateral neglect—Directional hypokinesia and bradykinesia. *Brain* **115,** 1849–1874 (1992).
10. Bisiach, E. Mental representation in unilateral neglect and related disorders: the twentieth Bartlett Memorial Lecture. *Q. J. Exp. Psychol.* **46A,** 435–461 (1993).
11. Kinsbourne, M. A model for the mechanism of unilateral neglect of space. *Trans. Am. Neurol. Assoc.* **95,** 143–145 (1970).
12. Posner, M. I., Walker, J. A., Friedrich, F. J. & Rafal, R. D. Effects of parietal injury on covert orienting of attention. *J. Neurosci.* **4,** 1863–1874 (1984).
13. Riddoch, M. J. & Humphreys, G. W. The effect of cueing on unilateral visual neglect. *Neuropsychologia* **21,** 589–599 (1983).
14. Heilman, K. M., Watson, R. T. & Valenstein, E. in *Clinical Neuropsychology* (eds Heilman, K. M. & Valenstein, E.) 243–293 (Oxford Univ. Press, New York, 1985).
15. Mattingley, J. B. & Driver, J. in *Parietal Lobe Contributions to Orientation in 3D Space* (eds Thier, P. & Karnath, H.-O.) 309–338 (Springer, Heildeberg, 1997).
16. Duncan, J. in *The Cognitive Neurosciences* (ed. Gazzaniga, M. S.) 721–733 (MIT Press, Cambridge, MA, 1995).
17. Husain, M. & Kennard, C. Visual neglect associated with frontal lobe infarction. *J. Neurol.* **243,** 652–657 (1996).
18. Husain, M., Shapiro, K., Martin, J. & Kennard, C. Abnormal temporal dynamics of visual attention in patients with spatial neglect. *Nature* **385,** 154–156 (1997).
19. Damasio, H. & Damasio, A. R. *Lesion Analysis in Neuropsychology* (Oxford Univ. Press, New York, 1989).
20. Mesulam, M.-M. *Principles of Behavioural Neurology. Tests of Directed Attention and Memory* (FA Davis, Philadelphia, 1985).
21. Bushnell, M. C., Goldberg, M. E. & Robinson, D. L. Behavioural enhancement of visual responses in monkey cerebral cortex. I. Modulation in posterior parietal cortex related to selective visual attention. *J. Neurophysiol.* **46,** 755–772 (1981).
22. Duhamel, J.-R., Colby, C. L. & Goldberg, M. E. The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* **255,** 90–92 (1992).
23. Andersen, R. A., Snyder, L. H., Bradley, D. C. & Xing, J. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annu. Rev. Neurosci.* **20,** 303–330 (1997).
24. Graziano, M. S. A., Gross, C. G. & Fernandez, T. A comparison of bimodal, visual-tactile neurons in parietal area 7b and ventral premotor cortex of the monkey brain. *Soc. Neurosci. Abstr.* **22,** 398 (1996).
25. Husain, M. in *Vision and Visual Dysfunction* Vol. 13 (ed. Stein, J. F.) 12–43 (Macmillan, Basingstoke, 1991).
26. Perenin, M.-T. & Vighetto, A. Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain* **111,** 643–674 (1988).

Acknowledgements. We thank J. Wade and A. Rudd, and the staff and patients of the stroke units at Charing Cross Hospital and St. Thomas' Hospital, London. This research was supported by the Stroke Association and the Wellcome Trust. J.B.M. was supported by a National Health and Medical Research Council (Australia) Neil Hamilton Fairley Fellowship, and by AMRAD Australia.

Correspondence and requests for materials to M.H. (e-mail: m.husain@cxwms.ac.uk).

Role of the NF-ATc transcription factor in morphogenesis of cardiac valves and septum

José Luis de la Pompa*, Luika A. Timmerman†, Hiroaki Takimoto*, Hiroki Yoshida*, Andrew J. Elia*, Enrique Samper*, Julia Potter*, Andrew Wakeham*, Luc Marengere*, B. Lowell Langille‡, Gerald R. Crabtree† & Tak W. Mak*

** The Amgen Institute, Ontario Cancer Institute, and Departments of Medical Biophysics and Immunology, University of Toronto, 620 University Avenue, Toronto, Ontario M5G 2C1, Canada*

† The Department of Developmental Biology, Stanford University Medical School Howard Hughes Medical Institute, 300 Pasteur Drive, Stanford, California 94305, USA

‡ Max Bell Research Centre, Toronto General Division, 200 Elizabeth Street, Toronto, Ontario M5G 2C4 and Department of Pathology, University of Toronto, Toronto, Ontario M5S 1A8, Canada

In lymphocytes, the expression of early immune response genes is regulated by NF-AT transcription factors[1,2] which translocate to the nucleus after dephosphorylation by the Ca^{2+}-dependent phosphatase, calcineurin[3]. We report here that mice bearing a disruption in the *NF-ATc* gene fail to develop normal cardiac valves and septa and die of circulatory failure before day 14.5 of