

Methods

The treatment of the monkeys was in accordance with the guidelines set by the US Department of Health and Human Services (NIH) for the care and use of laboratory animals.

Behavioural tasks. The behavioural task and physiological techniques used here have been described¹. Briefly, in each trial, a fraction of the dots moved coherently in one direction while the remaining dots appeared at random locations within the stimulus aperture, creating a masking motion noise. The strength of the coherent motion (per cent coherence) ranged from 0% (fully random noise) to 51.2%. Each trial began when the monkey fixated a small point of light on a video display (Fig. 1a). The monkey then viewed the random dot display for a brief interval while gazing steadily at the fixation point. Following a brief delay period, the monkey indicated the perceived direction of motion by making a saccadic eye movement to one of two visual targets corresponding to the two possible directions of motion. Extinction of the fixation point and appearance of the two visual targets signalled the end of the delay period. Eye movements were measured throughout all experiments by the scleral search coil technique¹⁸. The monkey received fluid rewards for correct choices.

Microstimulation techniques. For each microstimulation experiment, the multi-unit receptive field was mapped and the preferred direction identified using a bar of light or a patch of moving dots. To maximize the likelihood that the monkey would use directional information supplied by neurons at the stimulation site, the dot patterns were presented within the receptive field, and the axis of the directional discrimination was aligned with the preferred-null axis of the receptive field. Microstimulation (200 Hz, 10 μ A, biphasic pulses) was applied during the stimulus presentation interval or during the delay interval for monkey K, and also during a fixation interval before the onset of the visual stimulus ('previsual') for the other three monkeys (Fig. 1b). For monkeys R, S and T, each microstimulation interval lasted 800 ms; 200 ms separated stimulation intervals. For monkey K, microstimulation duration was 1 s with 500 ms separation between the two microstimulation intervals. In an extra ten experiments, monkey R was tested with same time course as monkey K; the results remained essentially the same as in Fig. 3c. The latter time course was also used in the red-green experiment. In the variable delay experiment (Fig. 4), microstimulation was applied in the last 800 ms of the delay period; the duration of the delay period was varied randomly among three values—900 ms (short), 1,800 ms (medium) and 2,700 ms (long).

Data analysis. Data were analysed using a standard logistic regression model¹⁹. Microstimulation effects were measured as the horizontal shift of the psychometric function in stimulated trials relative to control trials. The amplitude of this shift was measured in units of the abscissa (coherence, in percentage of dots), where leftward shifts were considered to be positive. Throughout this study, microstimulation did not significantly affect the slopes of the psychometric functions.

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Seeing only the right half of the forest but cutting down all the trees?

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Unilateral neglect following damage to the right hemisphere of the brain can be characterized by failure of the global attentional mechanisms of the right hemisphere to direct the local detail processors of the left hemisphere towards the contralesional left hemispace. This is suggested by patients who recognize the global form of the left side of shapes (the forest) but fail to cancel out its local details (the trees)¹. Here we report the opposite behavioural dissociation in a patient (Q.M.) with damage to the right hemisphere of the brain. Q.M. detected local details (such as the tail of a dog) on the left or right side of visual shapes, regardless of whether these details belonged to predefined target shapes (a dog in this case) or to distractor shapes differing on the opposite side (a dog with a swan's neck and head, for example). Psychological testing showed an abnormal tendency of this patient to respond to local features, but perfect accuracy in interpreting global features when the local features could not interfere in global processing. The results indicate that the left hemisphere can integrate multiple local features simultaneously but loses global awareness as soon as local features individually compete for response selection. However, accuracy of the whole is not necessary for the sequential processing of the parts.

Q.M. is a 57-year-old right-handed woman who suffered right-hemisphere ischaemia (Fig. 1). Two months after the stroke, the patient had severe contralesional neglect and hemianopia. We examined this patient extensively in light of the following observations. When presented with an array of 3s and Bs (Fig. 2a, test a1) and required to cancel out the 3s, Q.M. cancelled out both 3s and Bs on the right side of the array, disregarding the presence of the vertical bar on the left side of the Bs. Tilting the items and varying the thickness of the vertical bar (Fig. 2a, tests a2, a3) did not modify the patient's performance. Unexpectedly, the same behaviour was observed when the items were mirror-reversed about the vertical axis so that the difference between the two stimuli was on the right, not left, side. These findings were replicated using 6s and Ss (Fig. 2a, test b). When asked about her strategy, the patient answered that she looked for items with 'two little humps' when cancelling out Bs, and for items with an upper 'hook' when cancelling out 6s.

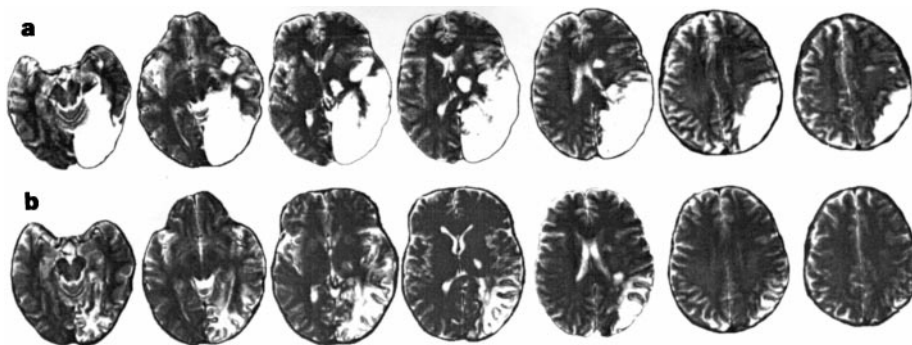


Figure 1 NMR scans of patient Q.M. Scans were taken at **a**, 5 days, and **b**, 15 days post-stroke. The right hemisphere lesion involves the occipital, temporal and parietal lobes (Brodmann's areas 17, 18, 19, 22, 37, 39 and 40) and the thalamic-capsular area. The patient's scores on a battery of tests¹² for assessment of

neglect were the following: line cancellation, 6 out of 21; letter cancellation, 14 out of 104; Wundt-Jastrow area illusion, 0 out of 20; sentence reading; 0 out of 6. Higher scores indicate better performance.

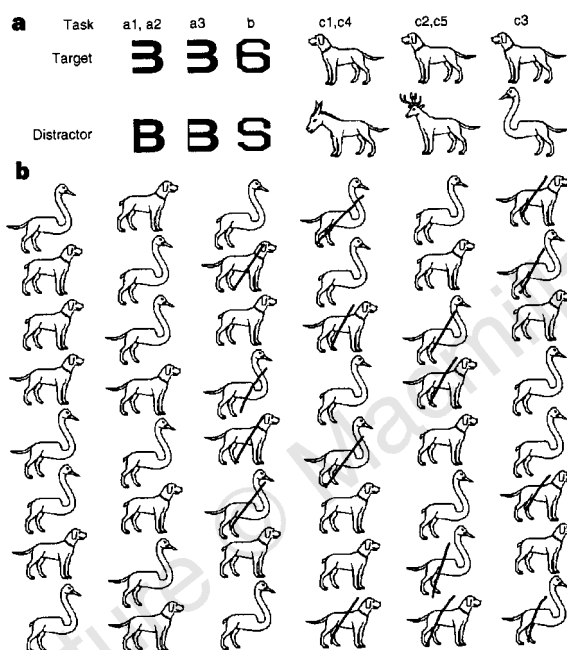


Figure 2 Cancellation tasks. **a**, Items of cancellation tasks a1–a3, b, and c1–c5. **b**, Example of Q.M.'s performance on task c3 (rightward-heading items). The ratios of frequencies of total cancelled targets to total cancelled distractors in the canonically oriented (can), mirror-reversed (mrev), leftward-heading (lhead) and rightward-heading (rhead) conditions were as follows: task a1 45:45 (can), 45:45 (mrev); task a2 39:39 (can), 42:42 (mrev); task a3 36:36 (can), 42:42 (mrev); task b 28:30 (can), 48:48 (mrev); task c1 16:16 (lhead), 16:16 (rhead); task c2 16:16 (lhead), 12:12 (rhead); task c3 16:16 (lhead), 18:18 (rhead); task c4 20:20 (lhead), 16:20 (rhead); task c5 16:10 (lhead), 16:15 (rhead).

Initially, the patient's behaviour might have been attributed to neglect based on object-centred coordinates²: in this case whatever the orientation of targets and distractors, which were items endowed with a canonical left–right orientation, the patient would have paid attention only their canonical right side, neglecting the left one. This hypothesis was ruled out by the finding that she treated items having no canonical left–right orientation in the same way that she treated 3s and 6s. When required to cancel out the line drawings of dogs with elongated tails (intermixed with short-tailed items), Q.M. omitted items on the left side of the array but cancelled out both long-tailed dogs and distractors such as a dog with a donkey's head and neck, a dog with a deer's head, or a chimaera consisting of half-dog and a half-swan (Fig. 2a, b, tests c1–c3). In

searching for critical detail (that is, the elongated tail), the patient disregarded the opposite half of the animal shape. This happened independently of the leftward or rightward orientation of the items and the type of array (rows by columns, tests c1–c3; scattered items, tests c4, c5). Q.M.'s performance could not be explained by the inability to recognize living items, as she correctly named (15 out of 15) line drawings of animals³. Object-centred neglect was not found in Q.M. when copying a multi-item scene⁴, in a shape-comparison task⁵ or when reading mirror-reversed words⁶.

These initial observations indicate the presence of both neglect for the contralesional space and exacerbated narrowing of attention towards local visual details. A pathological bias towards local processing was demonstrated by tachistoscopic testing with hierarchical Navon letters⁷ (Fig. 3a) presented in the right hemifield. When Q.M. had to pay attention both to local and global features, she showed a severe deficit in detecting global ones (divided attention task, Fig. 3c). The patient suffered from exaggerated local-on-global interference and slowing of global processing even when asked to actively disregard local features (global-directed attention task, Fig. 3b). However, Q.M. recognized with perfect accuracy the global shape of stimuli in which neutral local small rectangles could neither help nor interfere with the recognition of the global letter (Fig. 3a, b). This demonstrated the retained simultaneous integration of multiple local elements in the attended ipsilesional space when these elements could not compete for response selection. Lack of interference from local rectangles following damage of the right hemisphere could also have been related to the possible involvement of this hemisphere in the processing of local features based on non-living objects⁸.

We evaluated the processing of global and local visual features in the neglected space by presenting Q.M. with symmetrical and asymmetrical hierarchical shapes (Fig. 4a). Q.M. cancelled out all the local elements of all items, scanning each element by eye and head movements with the spared visual hemifield, but she never acknowledged the different global form of the left side of asymmetrical shapes. Q.M. was also asked to mark the centre of symmetrical and asymmetrical hierarchical shapes having a longer or shorter leftward extension (Fig. 4b). The centre of symmetrical shapes was marked with a negligible rightward shift from the true centre. This could have suggested effective analysis of global shape on both sides of space. However, the centre of the asymmetrical shapes was marked extremely close to the true centre of the symmetrical ones. This showed that the influence of the global contralesional extension of shapes was dramatically small. The centre of symmetrical and asymmetrical lines lacking any vertical component favouring the enlargement of the attentional focus (Fig. 4c) was marked with a severe rightward shift, irrespective of the leftward extension of the line.

Q.M.'s case shows that left unilateral neglect together with upregulated processing of local features does not necessarily impair the direction of attention towards the contralesional local components of hierarchical stimuli. Q.M.'s lesion spared the frontal areas in the damaged hemisphere. Therefore, the sequential detection of local elements might have been based on the access of the

posterior local processors of the left hemisphere to anterior pre-motor and motor control mechanisms in both hemispheres. On the other hand, Q.M.'s right hemisphere lesion destroyed the entire network of parietal, temporal and occipital areas activated by global processing in humans^{9,10}. This finding and the associated maintenance of integration of multiple local features in the ipsilesional space support the theory¹¹ that, in patients with left unilateral neglect, global processing can still be mediated by the intact left hemisphere. However, the cancellation and tachistoscopic tasks indicated that Q.M. was prone to the loss of conscious global attention as soon as local features competed for response selection. This result specifies, for the first time to our knowledge, a sharp functional limit of the left hemisphere in global processing, and provides a new view of the assignment of local and global processing to merely relative left and right hemispheric specialization^{9,10}.

Findings from positron emission tomography⁹ show that shifting attention between local and global features depends on the influence of parietotemporal areas on prestriate visual cortex. Our observations raise a related problem, namely, how to define mechanisms allowing the maintenance of conscious awareness at one attentional level, local or global, while processing the opposite

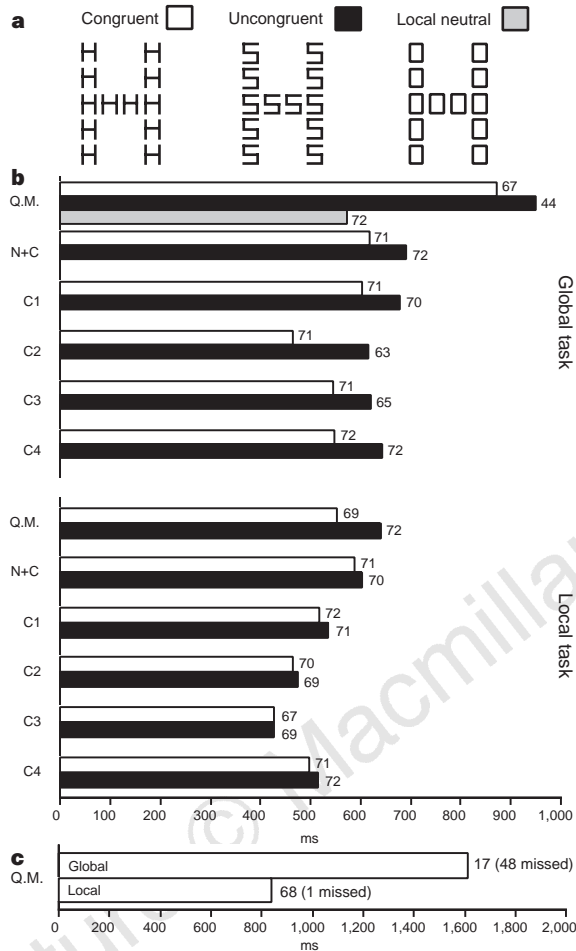


Figure 3 Bias towards local processing in patient Q.M. **a**, Examples of hierarchical Navon letters. **b**, Mean manual reaction times (in milliseconds) and frequencies of correct responses (in 72 trials; shown as numbers next to bars) of Q.M., of a control neglect patient (N + C) and of age-matched normal controls (C1–C4). In the direct attention task, Q.M. was slower (F-test $P < 0.001$) and less accurate (χ^2 test, $P < 0.01$) in the global than in the local task. In the global task: first, with incongruent stimuli Q.M.'s error frequency (in responding to local rather than global features, that is, local-on-global interference) was higher than that of the control subject (C2) with the worst performance (χ^2 test, $P < 0.001$); second, with congruent stimuli Q.M.'s performance was at ceiling (χ^2 test with continuity correction, $P > 0.5$); third, the perfect performance of Q.M. in the global task with local neutral features indicates that accuracy with congruent stimuli was probably not due to the processing of local, rather than global, features; and fourth, Q.M.'s reaction times were slower than the slowest control subject (N + C) (F-test, $P < 0.001$). In the local task: first, Q.M.'s performance did not differ from that of any control subject (χ^2 test, not significant in each comparison); and second, Q.M.'s reaction times were not statistically different from those of N + C and C1, and were slower than those of C2, C3 and C4 (F-test, $P < 0.001$ in each case). N + C (who correctly discriminated targets in the cancellation tasks with 3s, 6s and animals) had a parietal-frontal lesion which spared the posterior areas that were damaged in Q.M. **c**, Reaction times and frequencies of hits (and missed responses) in the divided attention tasks for Q.M. The detection of global targets was worse (χ^2 test, $P < 0.0001$) and slower (F-test, $P < 0.001$) than the detection of local ones.

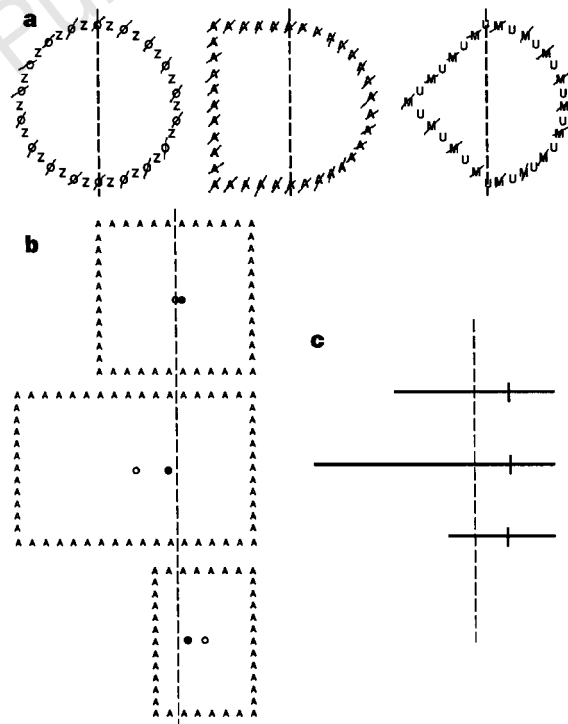


Figure 4 Processing of local and global visual features in the neglected space. **a**, Examples of cancellation by Q.M. of local elements of symmetrical and asymmetrical hierarchical shapes. **b**, Mean centre marking of hierarchical shapes. Open dot indicates true centre; filled dot indicates subjective centre. Taking the respective true centres as reference points, subjective centres were marked as follows: symmetrical shapes 2.8 mm rightward (t -test, $P < 0.01$), asymmetrical longer shapes 41.3 mm rightward (t -test, $P < 0.001$), asymmetrical shorter shapes 22.8 mm leftward (t -test, $P < 0.001$), asymmetrical shorter shapes 22.8 mm leftward (t -test, $P < 0.001$). Taking the true centres of symmetrical shapes as reference points, subjective centres were marked as follows: asymmetrical longer shapes 3.7 mm leftward, symmetrical shapes 2.8 mm rightward, asymmetrical shorter shapes 7.2 mm rightward (F omnibus test, $P < 0.001$). **c**, Mean rightward bisection error of asymmetrical longer, symmetrical, and asymmetrical shorter lines were, respectively, 39 mm, 40 mm and 37 mm (omnibus F test, not significant). The vertical dashed lines in **a–c** emphasize the relative position of items with respect to the patient's trunk midsagittal plane.

level. Q.M. exhibited a sort of transitory global simultanagnosia when attention was reflexively captured by local details which were relevant, but not sufficient, for task solution. Q.M.'s failure consciously to perceive the left half of the forest does not preclude her from cutting down all the trees one by one, but does not prevent her from failing to realize that she is cutting down the wrong woods. □

Methods

On cancellation tasks a1–a3 and b (Fig. 2), the items (2×2 cm) were arranged in an array of 9 rows \times 10 columns. In tasks a2 and a3, items were tiled 45° and 90° clockwise and anticlockwise. In tasks c1–c3, items (4×4 cm) were arranged in a 8×6 array. In tasks c4 and c5 the items were scattered. Each task was performed twice for each target/distractor and item orientation condition. A total of 60 targets and 60 distractors was presented in each orientation condition of tasks a and b; 24 targets and 24 distractors were presented in each condition of tasks c.

In the tachistoscopic Navon tests, stimuli (Fig. 3a) were large letters (global features, 4×6 degrees of visual angle) composed of smaller ones (local features, 0.8×1.2 degrees). In the divided attention task (Fig. 3c), stimuli were obtained by combining, between local and global levels, letters H, S, A and E; the same letter never appeared simultaneously at both levels. The patient had to detect H and S at whatever level they appeared. In the global- and local-directed attention tasks (Fig. 3b), congruent items were letters H and S composed of smaller letters H and S and incongruent ones were letters H and S composed of smaller letters S and H, respectively. In the global task, subjects discriminated between the large letter configurations (H or S); in the local task, the small letters were discriminated between. In the global task with local neutral features, stimuli were large letters H or S composed of small rectangles. Items were presented for 150 ms, with their inner edge at 1.5° to the right of central fixation.

The hierarchical stimuli of the recognition–cancellation task (Fig. 4a) were geometrical shapes (180×180 mm) composed of small letters (5×5 mm). Symmetrical stimuli were a circle ($n = 4$), a square ($n = 4$) and a diamond ($n = 4$). Asymmetrical stimuli ($n = 12$) were obtained by combining the half shapes of the symmetrical ones. In half of the trials, a target letter was alternated with a non-target letter.

In the centre-marking task (Fig. 4b), the items were symmetrical Navon squares (180×180 mm, $n = 12$) and asymmetrical Navon rectangles with longer (270 mm, $n = 12$) or shorter (120 mm, $n = 12$) horizontal leftward extensions. The items of the bisection task (Fig. 4c) were symmetrical (180 mm, $n = 12$) and asymmetrical (270 mm, $n = 12$; 120 mm, $n = 12$) lines.

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Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons

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Rapid information transfer within the brain depends on chemical signalling between neurons that is mediated primarily by glutamate and GABA (γ -aminobutyric acid), acting at ionotropic receptors to cause excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs), respectively. In addition, synaptically released glutamate acts on metabotropic receptors to excite neurons on a slower timescale through second-messenger cascades, including phosphoinositide hydrolysis¹. We now report a unique IPSP mediated by the activation of metabotropic glutamate receptors. In ventral midbrain dopamine neurons, activation of metabotropic glutamate receptors (mGluR1) mobilized calcium from caffeine/ryanodine-sensitive stores and increased an apamin-sensitive potassium conductance. The underlying potassium conductance and dependence on calcium stores set this IPSP apart from the slow IPSPs described so far^{2–4}. The mGluR-induced hyperpolarization was dependent on brief exposure to agonist, because prolonged application of exogenous agonist desensitized the hyperpolarization and caused the more commonly reported depolarization^{1,5,6}. The rapid rise and brief duration of synaptically released glutamate in the extracellular space can therefore mediate a rapid excitation through activation of ionotropic receptors, followed by inhibition through the mGluR1 receptor. Thus the idea that glutamate is solely an excitatory neurotransmitter must be replaced with a more complex view of its dual function in synaptic transmission.

Intracellular recordings were made in dopamine neurons of the ventral tegmental area (VTA) and substantia nigra. In the presence of ionotropic receptor antagonists, a train of stimuli (10 at 66 Hz) elicited a hyperpolarization that had two overlapping components of similar amplitude. The early component was mediated by GABA_B receptors (Fig. 1a), as previously reported⁷. The late component was insensitive to GABA_B antagonists (Fig. 1a, b) and reversibly blocked by tetrodotoxin (TTX, 300 nM; $91 \pm 2\%$, $n = 4$), suggesting that it might also be a slow IPSP.

The kinetics of this late hyperpolarization suggested that it was mediated by a mechanism distinct from GABA_B-mediated IPSP. The mGluR1-subtype is present on dopamine cells^{8,9}, is coupled to phosphoinositide (PtdIns) hydrolysis¹ and releases calcium from intracellular stores in other cells¹. Calcium could activate a calcium-sensitive potassium conductance (rSK3) present on dopamine cells that is sensitive to the bee venom toxin, apamin^{10,11}. Apamin irreversibly blocked the late hyperpolarization (by $86 \pm 3\%$, $n = 7$, Fig. 1a), but did not affect the GABA_B IPSP. Thus the late hyperpolarization was dependent on a rise in intracellular Ca²⁺ concentration and activation of a K⁺ current.

The mGluR antagonists (S)-MCPG (0.5–1.0 mM), (S)-4-CPG (500 μ M) and (RS)-AIDA (100–500 μ M) reduced the amplitude of the late hyperpolarization by $75 \pm 5\%$ ($n = 6$, Fig. 1b, c), $73 \pm 7\%$ ($n = 4$), and $44 \pm 8\%$ ($n = 6$), respectively. This pharmacological profile suggests that the late hyperpolarization is an IPSP mediated by mGluR1^{12–14} and the mGluR1 d splice variant has been specifically demonstrated in dopamine cells¹⁵. The inhibition caused was selective for the IPSP because (S)-MCPG and (S)-4-CPG did not affect the amplitude of the apamin-sensitive component of the after-hyperpolarization (AHP) following the action potential ((S)-