Abnormal Attentional Modulation of Retinotopic Cortex in Parietal Patients with Spatial Neglect

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Summary

Brain regions beyond visual cortex are thought to be responsible for attention-related modulation of visual processing [1, 2], but most evidence is indirect. Here, we applied functional magnetic resonance imaging (fMRI), including retinotopic mapping of visual areas, to patients with focal right-parietal lesions and left spatial neglect [3, 4]. When attentional load at fixation was minimal, retinotopic areas in right visual cortex showed preserved responses to task-irrelevant checkerboards in the contralateral left hemifield, analogously to left visual cortex for right-hemifield checkerboards, indicating a “symmetric” pattern in both hemispheres with respect to contralateral stimulation under these conditions. But when attentional load at fixation was increased, a functional asymmetry emerged for visual cortex, with contralateral responses in right visual areas being pathologically reduced (even eliminated for right V4/TEO), whereas left visual areas showed no such reduction in their contralateral response. These results reveal attention-dependent abnormalities in visual cortex after lesions in distant (parietal) regions. This may explain otherwise puzzling aspects of neglect [5, 6], as confirmed here by additional behavioral testing.

Results and Discussion

Visuospatial neglect is a severe neurological disorder that occurs after right-hemisphere damage, often involving parietal cortex [3, 4]. Neglect has multiple components [7], including losses of contralesional awareness that cannot be attributed to primary sensory or motor loss, but may involve pathological biases in attention [1, 8]. Neurally, this might reflect disruption of influences from damaged regions (e.g., parietal cortex) upon activity in intact visual areas [1, 2]. Recent functional neuroimaging in neglect patients showed some residual activation of intact visual cortex despite losses of awareness [9–11], as well as anomalies in remaining frontoparietal areas [12]. Evoked-potential studies [13] indicate that unperceived left visual stimuli may produce reduced or suppressed P1 and N1 components. But no study has directly tested whether neglect patients show abnormal attention-dependent activity in early, retinotopically mapped visual cortex, nor how the functional response of their visual cortex may depend on attentional demand [14, 15].

We used functional magnetic resonance imaging (fMRI), including retinotopic mapping of V1–V3 plus V4/TEO, to examine how task demand at central fixation may affect cortical responses to left visual field (LVF) or right visual field (RVF) stimulation after right-parietal damage. We selected two patients (AH and JC) with focal parietal lesions (Figure S1) but structurally preserved visual cortices and intact visual fields. They were scanned while performing tasks of minimal or increased attentional load at screen center. Previous work in normals shows that increasing attentional load at fixation can reduce visual activations for task-irrelevant peripheral stimuli, “symmetrically” for each hemifield [14]. Here, the low-load task was minimal (“no load”), simply requiring fixation on a central stream of colored stimuli. The higher-load task required discrimination of rare color targets in a similar central stream.

During either central task, checkerboards could appear in RVF, in LVF, or bilaterally, or none could appear (Figure 1A), in a pseudorandom blocked order that was counterbalanced across the two central tasks (see Experimental Procedures). We tested for any impact of attentional demand at central fixation on visual responses to peripheral task-irrelevant checkerboards, evoked in retinotopically mapped regions that corresponded to the checkerboard positions (Experimental Procedures). We predicted that visual responses to checkerboards should be relatively normal during the minimal task load (consistent with intact visual fields) but might exhibit a pathologically “asymmetric” pattern during increased task demand at fixation, with activation reduced in right visual cortex, unlike in left visual cortex.

Both patients showed similar fMRI results. We first examined effects of unilateral stimulation in LVF versus RVF (or vice versa) under minimal task load. Whole-brain statistical parametric maps (SPMs) revealed robust activation of contralateral occipital cortex that was symmetrical for the two hemispheres (Figures 1B and 1C), as normally expected. We next contrasted no load minus higher load (initially across checkerboard conditions). In both patients, higher load reduced visual activation in right occipitotemporal areas but had no such effect in left visual cortex (see Figure 1D). Increased demand...
at fixation thus introduced an “asymmetry” into the previously symmetric responses, diminishing activation of right visual cortex (responsive to LVF; Figure 1B), but not left visual cortex (responsive to RVF; Figure 1C).

We separately mapped visual areas in each hemisphere for each patient, applying established retinotopic procedures (see Experimental Procedures) to neglect patients for the first time. V1–V3 were readily identified along with V4/TEO in both hemispheres for both patients (Figure 2A), indicating preserved basic retinotopy (see also Figure S2) despite parietal damage and neglect. Activity estimates were extracted from each retinotopic area for the different conditions in the main load experiment (see Experimental Procedures) and submitted to two complementary assessments.

We first extracted z scores for peak voxels within each retinotopic area and hemisphere for the contrast between no load minus higher load in SPM (compare the whole-brain maps in Figure 1D). A striking asymmetry was apparent, with higher activity is observed in right occipital cortex under the no-load condition than in left, right, both, or neither hemifield in a pseudorandom order that was equivalent across the load tasks.

A robust contralateral visual response is observed for each hemisphere under no load, even on the right side where parietal damage exists (see arrows).

For both patients, the proportionalsize (see Experimental Procedures) of load effects on right-cortical responses to LVF checkerboards was maximal in V4/TEO (40%–95%), larger (all
For right V4/TEO, the response to contralateral left checkerboards (compared with none) was actually abolished under increased attentional load at fixation, with activation no longer differing significantly from the baseline condition with no peripheral stimuli (Figure 2B). Results for right retinotopic visual areas were similar for unilateral left and bilateral stimulation (i.e., for any condition driving contralesional LVF; see Figure S3), but they differed strikingly from the preserved response of left retinotopic areas to right checkerboards, even with increased load (compare Figures 2B and 2C), a finding that is again consistent with the whole-brain SPM results (Figure 1D). Left visual areas did not show such reduction during higher load, leading to a significant difference between hemispheres for the attentional effect on responses to contralateral stimuli (i.e., a hemisphere × load × stimulation interaction; see main text).

Finally, we used a similar attention-load paradigm for a behavioral study in six other neglect patients; in this paradigm, visual objects were now presented in LVF or RVF instead of checkerboards. Object recognition was tested after short runs of either central task, showing symmetric hit rates for LVF and RVF stimuli (35% versus 40%) after exposure under no load at fixation but significantly worse recognition for LVF (11%) than for RVF (28%) under higher load (see Supplemental Data). Again, this asymmetry appeared only under central load, analogously to our fMRI results.

Our results reveal pathological functional changes in distant, structurally intact retinotopic visual cortex for patients with neglect after right-parietal damage. These functional changes were attention dependent. Patients showed a normal symmetric pattern of visual activation in both hemispheres (for contralateral stimulation) under minimal load at fixation, but they showed a pathological asymmetry during increased demand at fixation. This led to reduction (or for right V4/TEO, even elimination) of the right-visual-cortex response to contralateral peripheral stimuli, whereas left visual cortex showed no such reduction. This asymmetry under increased attentional load at fixation is unlike the symmetric effects of central load in normals [14], even for higher task demands.

A notable result in our patients was that right V4/TEO became functionally “blind” to left checkerboards under higher attentional demand at fixation, a pattern never observed in healthy subjects [14], although normal attentional effects often increase across successive visual areas from V1 to V4/TEO [17–19]. The dramatic result for V4/TEO might conceivably relate to our color task, although this aspect alone cannot explain the pathological asymmetry of load effects. Future
studies could compare the impact of different types of load task, as well as different lesion sites in further patients. Our findings appear consistent with a major role for parietal cortex in attention [17, 18] and with the view that impaired awareness for contralateral visual stimuli in neglect patients may involve disturbed influences from higher areas upon sensory pathways [1, 2]. But although neglect is more frequent and severe after parietal damage, it can also arise after other lesions (e.g., frontal). Future work may determine whether such lesions can produce similar impacts on visual cortex and whether this involves concomitant changes in parietal activity [12].

Peripheral checkerboards were always task irrelevant here, although salient and not unexpected. Any account in terms of possible division of attention between center and periphery or in terms of limited resources in neglect patients would still need to explain the critical asymmetry found under high central load only. The damaged regions in right parietal cortex may normally serve to enhance visual processing [2, 17] when attentional load only. The damaged regions in right parietal cortex are salient and not unexpected. Any account in terms of distant from the lesion [2, 23], as shown here for attention approaches can reveal functional abnormalities in brain areas generally, our study illustrates that combining fMRI with lesion cortex versus left visual cortex in neglect patients. More critical consequences for functional responsivity of right visual cortex for contralesional visual stimuli in neglect patients may involve attentional-load experiment and two series of 64 scans for retinotopic mapping. A high-resolution T1 anatomical volume image (matrix: size: 256 × 176; voxel size: 1 × 1 × 1.5 mm³) was acquired in the same session. All time series from each individual were realigned, time corrected, and smoothed (4 mm FWHM) with SPM99 (http://fli.lion.ucl.ac.uk/spm/).

Whole-brain analysis was performed with the GLM as implemented in SPM [26]. For each patient, eight experimental conditions (two task loads × four peripheral stimulations) were modeled as boxcar waveforms convolved with a canonical hemodynamic response function for each scanning run (16 betas of interest per design matrix). Realignment parameters were entered as additional covariates to capture movement-related artifacts. Parameter estimates for each covariate were estimated for each voxel in each participant. Statistical parametric maps of the t-statistic (SPM(t)) were generated from linear contrasts between conditions, thresholded at p < 0.001 uncorrected, with cluster-size > 20 voxels.

Retinotopic-mapping data were analyzed with standard procedures [24, 25, 27], as described elsewhere [14], with SPM [26] and MrGray and MrFlatMesh software [28]. Retinotopic stimulation was first modeled with a GLM with two regressors (sine and cosine functions with the same frequency as stimulus wedges) plus movement parameters from image realignment. Phase maps were obtained for polar angle and eccentricity activation (arc tangent of sine/cosine ratio) with voxel-wise F-test at p < 0.001. Color-coded values were projected onto the flattened occipital cortical surface for identification of boundaries between discrete areas [24, 25, 27] with MrGray and MrFlatMesh [29]; see Figures S2A and S2B. Stimulus-responsive voxels were selected on the basis of the combination (overlap) of activation to both rotating and expanding stimulation. We could reliably delineate ventral and dorsal portions of V1, V2, V3, and ventral V4/TEO, with a similar number of voxels in both patients (total AH: 159 right, 168 left; JC: 138 right, 121 left) as in healthy subjects [14, 29].

Stimulus-responsive voxels in retinotopic areas were then projected back onto the original 3D brain volume (Figure 2A) for extraction of activation values (betas) during the attentional-load experiment. These betas were obtained from a new GLM analysis of the main load experiment, in which each successive stimulation epoch was now modeled separately (as an individual regressor), yielding eight betas (four epochs × two runs) for each of the four checkerboard conditions (bilateral, RFV, RVF, LVF, or none) in each of the two (higher-load or no-load) attention tasks (total 64 betas per patient). These betas were then averaged across voxels within each stimulus-responsive retinotopic region to yield a robust unbiased measure. Data from V1–V3 were averaged across upper and lower fields [17, 18] because these did not differ (one of the load experiments). Averaged beta values per area, hemisphere, condition, and epoch were submitted to ANOVA and t tests, with experimental conditions (load and stimulation) and ROI (visual area and hemisphere) as randomized factors (but we also ran another ANOVA treating the experimental conditions as repeat factors, which confirmed a similar outcome; see main text). Corresponding plots in Figures 2B and 2C had the no-checkerboard condition subtracted from them. In addition, to estimate the relative (proportional) size of load effects on different visual areas, we computed the mean difference between low load conditions minus high load conditions, normalized by response magnitude in the low-load

**Experimental Procedures**

**Patients in Neuroimaging Study**

Two patients with right-hemisphere stroke were selected because of their focal lesions in right parietal cortex (Figure S1), their left spatial neglect but intact visual fields, and their preserved ability to maintain fixation during scanning. Neglect was diagnosed with standard tests at the time of fMRI investigation (Table S1).

**Attentional Task during Scanning**

The paradigm was similar to recent work in healthy subjects [14], though easier tasks were used as appropriate for neurological patients. Two successive experimental runs (~12 min each) each comprised no-load and higher-load tasks, with their order counterbalanced across runs. Central Ts or Os appeared equiprobably across checkerboard conditions for 500 ms each (separated by 250 ms), with color and T orientation pseudorandomized. An instruction display (10 s) preceded each task block. Target onsets in the higher-load condition (red Ts) were unpredictable (7.5% of items, equiprobable across checkerboard conditions). Both patients showed accurate performance (AH 98% correct, JC 90% correct). During each task, large checkerboards (~10 × 14°, sparing central 2° on either side) flickered (8 Hz) for epochs of 20 s in LVF, RVF, both sides, or neither, in pseudorandom sequence (each appeared once in an otherwise random order, with a different random sequence of the four peripheral-stimulation conditions during each task block, but the actual order of the four peripheral-stimulation conditions was identical overall for the two different load tasks). Each checkerboard condition (LVF, RVF, bilateral, or none) arose four times during each task in each run, thus eight times in total. In other words, the full set of conditions was essentially repeated eight times per patient. Patients were instructed to ignore the checkerboards. Three 20 s empty periods (resting baseline) were included before and after each task. Continuous eye tracking during fMRI confirmed correct central fixation across conditions (see Supplemental Data).

**Retinotopic Mapping**

A standard visual-mapping protocol was administered after the attentional tasks, comprising two separate runs as described elsewhere [14]; see also [24, 25]. Stimulation by rotating checkerboard wedge (45° angle) was used for mapping polar angle, whereas an expanding annulus mapped eccentricity up to 14° from the center of field (0.02 Hz period), sparing the central 2° on each side in both cases. Retinotopic stimulation (rotation or expansion) traversed the same parts of the visual field in which peripheral checkerboards were presented during the load task [14] so that we could assess attentional modulations specifically for stimulus-driven retinotopic regions (as defined by individual mapping) in the separate load experiment. Fixation was maintained on a colored dot at screen center during mapping, as confirmed by online eye tracking.
condition (initially averaged across all conditions with contralateral stimuli, i.e., LVF and bilateral for right visual cortex, RVF and bilateral for left visual cortex; however, see Figure S3 for separation of unilateral and bilateral results). Finally, within each retinotopic area, we also extracted the peak z score (see Table S2) obtained for the contrast of no load minus higher load in the initial whole-brain SPM analysis (in which only one beta value had been estimated for each of the experimental conditions per run).

Supplemental Data

Supplemental Data include Supplemental Experimental Procedures, two tables, and three figures and can be found with this article online at http://www.current-biology.com/supplemental/S0960-9822(08)01263-3.

Acknowledgments

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In the legend to Figure 1 of this paper, the text cites the wrong panel here, where “A” should be “B”:

“(B and C) Whole-brain SPM maps in patients AH and JC showing activation under no load in (A) right occipitotemporal cortex for LVF > RVF checkerboards or (C) activation of left occipitotemporal cortex for RVF > LVF checkerboards.”

The journal regrets this error.

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Supplemental Experimental Procedures

Follow-up behavioural experiment

Six additional patients with right-hemisphere lesions, left spatial neglect, and intact visual fields performed two tasks at central fixation, equivalent to the no-load and higher-load conditions in the main fMRI session. These now ran in short alternating blocks (20–40 sec), while object pictures[1] were briefly flashed (250 ms) at unpredictable intervals (every 5–10 sec) in either the left or right hemifield (2–4 pictures on each side during each block type). No response to these objects was required on presentation (analogously to the checkerboards during fMRI). After each pair of blocks (in counterbalanced order, i.e., no-then-high or high-then-no load), recognition was tested by presenting (centrally) the previously shown objects one a time but now intermingled in a sequence with novel items (12 each). Patients had to make an old/new judgment for each of these centrally-presented items. Four to five pairs of blocks were administered to each patient, in different order (after a first pair used for training in the central tasks only, with no surprise recognition test).

The recognition tests revealed that hit-rate was comparable for objects previously exposed in LVF or RVF (35% and 40% respectively) under no-load at fixation; but that higher central load during exposure led to significantly worse recognition for LVF (now 11%) than RVF stimuli (28%). The interaction between
central demand and hemifield was reliable across the six patients ($F_{1,5}=7.5$, $p=.04$). Analogously to the fMRI data, there was thus no difference between visual hemifields under minimal central load ($t_{5}=0.5$, n.s), with a visual asymmetry emerging only under increased central load ($t_{5}=3.9$, $p=0.01$).

**Eye-tracking during scanning**
Continuous eye-tracking was performed during fMRI via infrared camera (ASL 450 LRO system, 60 Hz sampling rate). Data analyzed offline showed correct fixation on the central stimulus stream across all conditions of the attention experiment, as expected given task requirements (mean variance of eye position < 1.15° of visual angle; deviation > 2 degrees away from centre arose only <5.75% of time points, in each patient). Most importantly, eye-position was equivalent across conditions, with a 4 (stimulation) x 2 (task load) ANOVA on mean eye-position coordinates (x or y) showing no significant main effect nor interactions for horizontal (all $F<1.33$, $p>.26$) or vertical eye-position (all $F<1.67$, $p>.12$). Similarly, for the retinotopic stimulation runs, offline analyses of eye-tracking data showed accurate central fixation and no differences in mean gaze position between the two mapping situations, for both patients.

**Supplemental Reference**
**Table S1:**
Clinical data for each patient in the fMRI study.

<table>
<thead>
<tr>
<th></th>
<th>Patient AH</th>
<th>Patient JC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic details</strong></td>
<td>Male, 59 year-old, right-handed</td>
<td>Male, 72 year-old, right-handed</td>
</tr>
<tr>
<td><strong>Type and time of stroke</strong></td>
<td>Ischemic infarction, 5 months post-onset</td>
<td>Hemorrhage, 2 months post-onset</td>
</tr>
<tr>
<td><strong>Neurological deficits</strong></td>
<td>Mild paresis of left arm, no hemianopia, but left neglect</td>
<td>Mild paresis of left hand, no hemianopia, but left neglect</td>
</tr>
<tr>
<td><strong>Letter cancellation task</strong></td>
<td>6 omissions / 30 left-sided targets</td>
<td>8 omissions / 30 left-sided targets</td>
</tr>
<tr>
<td><strong>Line bisection task</strong></td>
<td>Mean rightward deviation 12 mm for 200mm line</td>
<td>Mean rightward deviation 21 mm for 200mm line</td>
</tr>
</tbody>
</table>
Table S2:
Peaks of load effects within retinotopic ROIs
(for contrast of No Load > Higher Load in initial SPM analysis)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right hemisphere</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>z-score</td>
<td>p-value</td>
</tr>
<tr>
<td>AH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>2.53</td>
<td>0.006</td>
</tr>
<tr>
<td>V2</td>
<td>3.28</td>
<td>0.001</td>
</tr>
<tr>
<td>V3</td>
<td>3.26</td>
<td>0.001</td>
</tr>
<tr>
<td>V4</td>
<td>3.61</td>
<td>0.000</td>
</tr>
<tr>
<td>JC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>3.49</td>
<td>0.000</td>
</tr>
<tr>
<td>V2</td>
<td>3.36</td>
<td>0.000</td>
</tr>
<tr>
<td>V3</td>
<td>2.77</td>
<td>0.003</td>
</tr>
<tr>
<td>V4</td>
<td>3.55</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Figure S1.
Anatomy of brain lesions in each patient. Both AH and JC had persistent left spatial neglect after focal right parietal damage (see also Suppl. Table S1). Upper panels: 3D reconstruction of cortical surface (dotted circles indicate the lesions), with oblique view on posterior right hemisphere. Lower panels: horizontal sections (arrows indicate the lesions), with right hemisphere shown on left, following radiological convention. Both lesions also extend subcortically, beyond visible damage to the cortical surface.
Figure S2.
Illustration of retinotopic mapping data for both hemispheres and both patients, projected on flattened views of the occipital cortical surface. These flatmaps are
shown here for completeness, since the present study is the first to our knowledge to apply retinotopic mapping in neglect patients. The flatmap data were visualized by combining SPM data with MrGray and MrFlatMesh routines developed by Wandell and colleagues (see Dougherty et al., 2003; Schwarz et al., 2005). Note that our mapping procedure used a standardized short stimulation session (equivalent to that used in normals by Schwartz et al., 2005) that was tolerable for patients, with the aim just to obtain satisfactory demarcation of distinct visual areas, V1, V2, V3 and V4/TEO (but not to measure magnitude or extent of retinotopic activation per se). The rotating wedge and expanding annulus used for retinotopic mapping traversed the same visual angles that could be occupied by checkerboards in the main attention-load experiment (see also Schwartz et al., 2005). Importantly here, mapping results for right visual areas (damaged hemisphere, R) were qualitatively similar to those for left areas (intact side, L). Stimulus-responsive voxels for analysis in the main experiment were selected based on the combination (overlap) of activations to both rotating and expanding stimulations in the visual field (see black outlines of each area in this figure). The mapping data are displayed here with colour codes corresponding to (A) polar angle (i.e. rotation phase of the wedge) or separately (B) eccentricity (i.e. expansion phase of the annulus). Additional analyses (not shown) separated fMRI data for retinotopic ROIs from the main attentional-load experiment in terms of different eccentricity sectors, near or far from central fixation (as in Schwartz et al., 2005). This confirmed that the asymmetrical impact of attentional load (i.e. higher central load reducing visual responses for right visual cortex but not left in neglect patients) applied across all eccentricities here, as per our main analysis that disregards that factor.
Figure S3.
Response of retinotopic areas in right visual areas (beta values, relative to the no-checkerboard baseline, analogous to Fig 2b in main paper) for all conditions with contralateral visual stimulation (unilateral or bilateral checkerboards, now shown separately here), as a function of attentional-load at fixation. In both patients, increased attentional-load reduced the response to contralateral checkerboards in right visual cortex, leading even to elimination of any visual response in right V4/TEO. This was found similarly for unilateral left and bilateral stimulation (i.e., for both conditions that included a left checkerboard projecting to right visual cortex).