Functional Imaging of the Human Lateral Geniculate Nucleus and Pulvinar

Sabine Kastner, Daniel H. O’Connor, Miki M. Fukui, Hilda M. Fehd, Uwe Herwig, and Mark A. Pinsk

Department of Psychology, Center for the Study of Brain, Mind, and Behavior, Princeton University, Princeton, New Jersey 08544

Submitted 8 June 2003; accepted in final form 16 September 2003

J Neurophysiol 91: 438–448, 2004. First published September 17, 2003; 10.1152/jn.00553.2003. In the human brain, little is known about the functional anatomy and response properties of subcortical nuclei containing visual maps such as the lateral geniculate nucleus (LGN) and the pulvinar. Using functional magnetic resonance imaging (fMRI) at 3 tesla (T), collective responses of neural populations in the LGN were measured as a function of stimulus contrast and flicker reversal rate and compared with those obtained in visual cortex. Flickering checkerboard stimuli presented in alternation to the right and left hemifields reliably activated the LGN. The peak of the LGN activation was found to be on average within ±2 mm of the anatomical location of the LGN, as identified on high-resolution structural images. In all visual areas except the middle temporal (MT), fMRI responses increased monotonically with stimulus contrast. In the LGN, the dynamic response range of the contrast function was larger in its inferior, lateral, and medial subdivisions several visual areas that receive projections from striate and extrastriate visual cortex (Maunsell and Van Essen 1983; Standage and Benevento 1983; Ungerleider et al. 1983, 1984). The functions of the pulvinar are not well understood. It has been shown that the majority of neurons in retinotopically organized areas of the pulvinar are responsive to a variety of visual stimulus properties such as orientation or direction of movement but without much specificity (Petersen et al. 1985). In other areas of the pulvinar less well defined by retinotopy, neural responses have been related to complex behavior such as selective visual attention (Robinson and Petersen 1992).

In the human brain, it has proven difficult to study subcortical nuclei because of spatial resolution and signal-to-noise limitations of brain-mapping techniques. Thus far, reliable fMRI activation of the human LGN has been demonstrated at high magnetic field strength (Chen and Zhu 2001; Chen et al. 1998a,b, 1999; O’Connor et al. 2002). A retinotopic organization of the human LGN similar to that in macaques was suggested in a high-resolution fMRI study that demonstrated distinct activations associated with stimulation of the upper and lower visual field in the inferior and superior parts of the LGN, respectively (Chen et al. 1999). Other studies have shown that neural responses in the LGN can be modulated by top-down processes related to selective attention and mental imagery (Chen et al. 1998b; O’Connor et al. 2002). Here, we investigated the functional anatomy and basic response properties of the human LGN and attention-related activation in the pulvinar. Collective responses of neural populations in the LGN were measured as a function of stimulus contrast and flicker reversal rate and compared with population responses obtained in visual cortical areas. Activity in the pulvinar was probed under different sensory and attention conditions. Our studies demonstrate that fMRI at 3 T can be used effectively to study thalamocortical circuits in the human brain.

INTRODUCTION

The topography and functional organization of human visual cortex have been studied in recent years using functional brain imaging, in particular functional magnetic resonance imaging (fMRI). Several visual areas have been delineated based on their retinotopic organization (DeYoe et al. 1996; Engel et al. 1997; Sereno et al. 1995). In retinotopically organized areas, neural responses evoked by stimuli varying along dimensions such as luminance contrast (Boynton et al. 1996), motion (Tootell et al. 1995), color (Beauchamp et al. 1999; Hadijikhami et al. 1998; McKeefry and Zeki 1997), and texture (Kastner et al. 2000) have been characterized. Surprisingly little is known, however, about the functional anatomy and response properties of subcortical nuclei containing visual maps, such as the lateral geniculate nucleus (LGN) or the pulvinar.

The LGN is the thalamic station in the projection of the visual pathway from retina to primary visual cortex. The anatomy of the LGN and response properties of its neurons have been extensively studied in nonhuman primates (for reviews see Jones 1985; Sherman and Guillery 2001). The LGN is organized into 6 layers, each of which receives input from either the contra- or ipsilateral eye. There are 4 dorsal LGN layers containing small (parvocellular, P) neurons that are characterized by sustained discharge patterns, sensitivity to color, and low contrast gain, and 2 ventral layers containing large (magnocellular, M) neurons that are characterized by transient discharge patterns and high contrast gain (Creutzfeldt et al. 1979; Dreher et al. 1976; Mergan and Maunsell 1993; Shapley et al. 1981; Wiesel and Hubel 1966).

The pulvinar is located in the dorsal thalamus and contains in its inferior, lateral, and medial subdivisions several visual areas that receive projections from striate and extrastriate visual cortex (Maunsell and Van Essen 1983; Standage and Benevento 1983; Ungerleider et al. 1983, 1984). The functions of the pulvinar are not well understood. It has been shown that the majority of neurons in retinotopically organized areas of the pulvinar are responsive to a variety of visual stimulus properties such as orientation or direction of movement but without much specificity (Petersen et al. 1985). In other areas of the pulvinar less well defined by retinotopy, neural responses have been related to complex behavior such as selective visual attention (Robinson and Petersen 1992).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: S. Kastner, Department of Psychology, Center for the Study of Brain, Mind, and Behavior, Princeton University, Green Hall, Princeton, NJ 08544 (E-mail: skastner@princeton.edu).
METHODS

Subjects

Nine subjects (6 males; age: 21–38 yr) participated in the study, which was approved by the Institutional Review Panel of Princeton University. Six subjects each participated in experiments 1 and 2, 5 in experiment 3, and 4 in experiment 4. All subjects were in good health with no past history of psychiatric or neurological diseases and gave their informed written consent. Subjects had normal or corrected-to-normal visual acuity.

Visual stimuli and experimental design

Visual stimuli were generated on a Macintosh computer. In experiments 1–3, checkerboard stimuli were presented to the right or left visual hemifield. In experiment 4, checkerboard stimuli were presented simultaneously to both hemifields. In all experiments, a central fixation cross was present. Stimuli had a mean luminance of 271 cd/m² and subtended a visual angle of 12.5° horizontally and 12° vertically. The central 1.5° of the stimulus and regions along the vertical meridian were spared (Fig. 1A). Checks had a 1.5° width and a length expanding radially from 0.5° closest to fixation to 5° for the most peripheral checks; the spatial frequency of the checkerboard ranged from 0.1 to 1 cycle/deg. In all experiments, the subjects’ task was to maintain fixation at the central fixation cross and to passively view the stimuli. In experiment 4, subjects also performed a spatial-attention task, described below. In 1–2 sessions held before scanning, subjects were trained to perform the fixation task and the spatial-attention task for several minutes without deviating from fixation. Eye movements were monitored by a head-mounted infrared eyetracking system (ISCAN ETL-500; Iscan, Burlington, MA) during these sessions. There was no significant difference in eye position between periods of attention to the left and to the right of fixation, or between the different sensory conditions during fixation tasks. Eye position almost never left the blank region surrounding the fixation cross, that is the central 1.5° (99.86% of samples were within this region), and analysis of those samples falling outside the region showed no relation between these locations and the attention or sensory conditions (for a more detailed description of eye movement control experiments, see O’Connor et al. 2002).

Experiment 1 was designed to localize the LGN and study its functional anatomy. Checkerboard stimuli of high contrast (100%) that reversed luminance at 7.5 Hz were presented in alternation either to the left or the right visual hemifield in 6 blocks of 16 s. Each of the 6 test runs started and ended with a 24-s presentation block of a fixation cross on a blank gray screen. Experiment 2 was designed to derive contrast response functions for the LGN and visual cortex. All parameters were as in experiment 1 except for the contrast of the checkerboard stimuli. Checkerboard contrast was defined as the maximum luminance minus the minimum luminance, divided by twice the mean. Six different contrast levels were investigated: 4, 9, 35, 50, 67, and 100%. The different contrast levels were verified by direct photometer measurements from the projection screen. Within a run, blocks of stimuli at a given contrast level were either presented at increasing or decreasing contrast levels, counterbalanced within a scanning session. One block of stimuli was presented for each contrast level and hemifield per run. Each of the 12 test runs started and ended with a 24-s presentation block of a fixation cross on a blank gray screen.

Experiment 3 was designed to measure responses as a function of flicker rate for the LGN and visual cortex by varying the reversal rate of the checkerboard stimulus. All other parameters were as in experiment 1. Three different reversal rates were used: 0.5, 7.5, and 20 Hz. Within a run, each flicker rate was presented once to each hemifield in pseudo-randomized order. Each condition was repeated 12 times during a scanning session. Experiment 4 was designed to investigate modulation of visually evoked responses by selective attention in the LGN and pulvinar. A high-contrast checkerboard reversing luminance at 7.5 Hz was presented simultaneously to both hemifields in blocks of 18 s, interleaved with blank periods of the same duration. The central 1.5° of the stimulus and regions along the vertical meridian were spared. Subjects were instructed to covertly direct attention to the checkerboard arc at 10° eccentricity and to detect randomly occurring luminance changes along that arc. Covert attention shifts were indicated by briefly presenting an arrow at fixation that pointed to the left or right hemifield 1 s before the onset of the stimuli. In a second variant of the experiment, 2 subjects were tested with the same visual paradigm, but asked to simply maintain fixation and passively view the bilateral checkerboard stimuli instead of performing the covert attention task. In a third variant of the experiment, 4 subjects were tested while directing attention to checkerboard stimuli presented unilaterally in alternation to the right or left hemifield in blocks of 16 s (for details of attention tasks, see O’Connor et al. 2002). We reported attention-related modulation of LGN activity for these and other attention paradigms elsewhere (O’Connor et al. 2002) and will focus here on results for the pulvinar.

Data acquisition and analysis

General scanning and data analysis procedures were identical in all experiments. Images were acquired with a 3 T head scanner (Allegra, Siemens, Erlangen, Germany) using a standard head coil. Subjects were comfortably placed on their backs with their heads surrounded by soft foam to reduce head movements. Data were acquired in 24 scan sessions, each lasting about 2 h. In addition, retinotopic mapping was performed for all subjects in a separate scan session. Functional images were taken with a gradient echo, echo planar sequence (TR = 2 s, TE = 30 ms, flip angle = 90°, 64 × 64 matrix). Twenty-two

![Fig. 1. Functional activation of the lateral geniculate nucleus (LGN) and visual cortex. A–D: individual results from 4 subjects tested in experiment 1. Checkerboard stimuli of high contrast that reversed luminance at 7.5 Hz were presented in alternation to the left or right of a central fixation (+) cross in blocks of 16 s (A). Checkerboard stimuli presented to the right hemifield activated the left LGN and visual cortex (yellow-orange); those presented to the left hemifield activated the right LGN and visual cortex (green-blue). For each subject, activated regions are shown in axial and coronal planes. Scale indicates Z-score values of functional activity in colored regions. R, right hemisphere; L, left hemisphere.](image-url)
contiguous, axial slices (thickness = 3 mm, gap = 1 mm, in-plane resolution: 3.17 × 3.17 mm) were acquired in 6 to 12 series of 78 to 152 images each, covering the thalamus and visual cortex. Echo-planar images were compared with a co-registered high-resolution anatomical scan of each subject’s brain taken in the same session (FLASH, TR = 150 ms, TE = 4.6 ms, flip angle = 90°, 256 × 256 matrix). Another high-resolution anatomical scan of the whole brain (MPRAGE sequence; TR = 11.1 ms; TE = 4.3 ms; flip angle = 8°; matrix 256 × 256 voxels; 3-dimensional resolution, 1 mm3) was taken for detailed anatomical-functional analyses.

Visual stimuli were projected with an Epson LCD projector onto a translucent screen located at the back of the scanner bore at a distance of 60 cm from the subjects’ eyes. Stimuli were viewed from inside the bore of the magnet by a mirror system attached to the head coil, providing a maximal visual angle of 28° × 36°.

All analyses were performed on data sets from single subjects. Between-scan head movements were corrected by aligning each image to a reference image obtained in the middle of the session using Automatic Image Registration (AIR) software (Woods et al. 1993). Statistical analyses were restricted to brain voxels with adequate signal intensity (average intensity of >20% of the maximum value across voxels). The first 5 images of each scan were excluded from analysis. Statistical analyses were performed using multiple regression in the framework of the general linear model (Friston et al. 1995) with National Institutes of Health functional imaging data analysis program (FIDAP) software. In experiments 1–3, a square wave function reflecting the contrast of left versus right visual hemifield stimulation was convolved with a Gaussian model of the hemodynamic response (lag 4.8 s, dispersion 1.8 s) to generate an idealized response function that was used in the regression model. In experiment 4, bilateral checkerboard presentations were contrasted with blank presentations. Additional regressors were used to factor out variance attributed to between-run changes in mean intensity and within-run linear changes. With these statistical models, foveal stimulus representations were excluded from further analysis; in all experiments, fMRI activity reflects only activity evoked by the peripheral checkerboard stimuli. Statistical maps were thresholded at a Z-score of 2.33 (P < 0.01, corrected for multiple comparisons) and overlaid on structural T1-weighted scans taken in the same session and in the same plane. LGN activations were identified based on contiguous voxels in its anatomical location (e.g., Fig. 1; Table 1). Activity in visual cortex was assigned to retinotopically organized areas (see following text).

For each subject, time series of fMRI intensities were averaged over all voxels activated in a given visual area during visual stimulation versus blank presentations. Mean signals were computed by averaging across all intensity values obtained in a given condition and are given as percentage signal change (% change), which was computed relative to the mean of the 6 intensity values preceding a visual stimulation period. Because no differences between activity in the right and left LGN and visual cortex were found, data were combined across hemispheres. Time series data and mean signal changes were averaged across subjects and are presented as group data. Statistical significance was determined by repeated-measures ANOVAs on all intensity values obtained in a given condition. Contrast and flicker rate response functions were computed based on mean signal changes and normalized to the responses evoked by the 100% contrast stimulus or 20-Hz stimulus, respectively. Contrast response functions (CRFs) were derived separately for presentation conditions of increasing and decreasing contrast. For each area in which CRFs did not differ in the 2 presentation conditions, data were combined. Only in area MT were significant differences in CRFs found; the data for MT are reported separately. A contrast modulation index (CMI) was computed to quantify the sensitivity of each visual area to modulation by contrast. The CMI was defined as follows: CMI = (R MaxC – R MinC)/(R MaxC + R MinC); MaxC = maximum contrast level (=100%), MinC = minimum contrast level (=4%), R = Response. CMI values close to 1 indicate strong modulation of neural responses by stimulus contrast; values close to 0 indicate weak modulation. Statistical significance of index values was determined by ANOVAs and t-test. For each subject, statistical maps and structural images were transformed into Talairach space (Talairach and Tournoux 1988) using BrainVoyager software.

Mapping visual areas

Retinotopic mapping was performed for each subject in a separate scanning session using procedures similar to those established by Sereno et al. (1995) and described in detail in Kastner et al. (2001). Briefly, areas V1, V2, ventral and dorsal V3 (referred to as V3), and V3A were identified by the alternating representations of the vertical and horizontal meridians, which form the borders of these areas (e.g., DeYoe et al. 1996; Engel et al. 1997; Sereno et al. 1995). Areas V4 and TEO were identified by their characteristic upper (UVF) and lower (LVF) visual field retinotopy (Kastner et al. 1998, 2001). Area V4 in this study likely corresponds to area V4 of McKeefry and Zeki (1997) and Wade et al. (2002) and appears to overlap with V4v and V8 described by Hadjikhani et al. (1998). Area TEO likely corresponds to area CoS described by Malach et al. (2002). Activations in area MT were identified based on the characteristic anatomical location of this area (Tootell et al. 1995; Watson et al. 1993) and confirmed in 4 subjects with a standard functional motion localizer (radially moving dots vs. stationary dots). Because our statistical analysis compared left versus right hemifield presentations, activa-

## Table 1. LGN: Talairach coordinates and activated volumes

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Subject</th>
<th>Right</th>
<th>Left</th>
<th>Volume, mm3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical</td>
<td>S1</td>
<td>22</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>22</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>S3</td>
<td>22</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>S4</td>
<td>18</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>S5</td>
<td>21</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>S6</td>
<td>21</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>23</td>
<td>21</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Localizer (Exp. 1)</th>
<th>Subject</th>
<th>Right</th>
<th>Left</th>
<th>Volume, mm3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>24</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>22</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>S3</td>
<td>22</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>S4</td>
<td>18</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>S5</td>
<td>21</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>S6</td>
<td>21</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>23</td>
<td>21</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contrast (Exp. 2)</th>
<th>Subject</th>
<th>Right</th>
<th>Left</th>
<th>Volume, mm3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>21</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>23</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>S3</td>
<td>23</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>S5</td>
<td>19</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>S8</td>
<td>20</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>21</td>
<td>24</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency (Exp. 3)</th>
<th>Subject</th>
<th>Right</th>
<th>Left</th>
<th>Volume, mm3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>22</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>23</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>S3</td>
<td>24</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>S4</td>
<td>22</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>S7</td>
<td>24</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>23</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

S = subject.
stimuli presented to the right hemifield studied using fMRI. Mean fMRI responses were 1.2% signal change (±0.2 SE) in the LGN and 2.0% signal change (±0.1 SE) in visual cortex, averaged across all presentation blocks, hemispheres, and subjects.

The location of the LGN in Talairach space was determined by performing 2 separate analyses. First, the LGN was identified in each subject on high-resolution anatomical images, where it appeared as a small region of increased signal intensity superior to the hippocampal formation (Table 1, "Anatomical"; Horton et al. 1990). Second, the center of mass of the functional activity in the LGN was determined for each subject and each experiment (Table 1). The mean anatomically defined Talairach coordinates across all subjects and experiments were (x = 23, y = −21, z = −5) for the right LGN and (x = −21, y = −23, z = −5) for the left LGN. In close correspondence to these data, the mean functionally defined Talairach coordinates across all subjects and experiments were (x = 22, y = −22, z = −4) for the right LGN and (x = −21, y = −23, z = −4) for the left LGN. The locations of the functional LGN activations were also found to be highly reliable across the 3 different experiments for each of the 3 subjects that were tested in all experiments (Table 1, S1–S3). The mean activated volume was 244 mm$^3$ (±28 SE) in the right LGN and 234 mm$^3$ (±29 SE) in the left LGN, averaged across all subjects and experiments. The right and left LGN were activated to a similar degree in terms of volume and signal amplitude; no significant differences between hemispheres were obtained.

Responses as a function of stimulus contrast in the LGN and visual cortex

In experiment 2, fMRI signals evoked by checkerboard stimuli varying in contrast were investigated in the LGN and compared with those obtained across visual cortex. Checkerboard stimuli at 6 different contrast levels ranging from 4 to 100% were presented in blocks at either increasing or decreasing contrast during a given run. Data were analyzed separately for the 2 presentation conditions and then combined for areas in which no significant difference was found. This was the case for the LGN and all visual cortical areas except MT, for which results of the 2 presentation conditions are reported separately (see following text). Time series of fMRI signals evoked by checkerboard stimuli presented at 4, 9, 35, and 100% contrast, averaged across scans and subjects, are presented for the LGN, V1, V4, and MT in Fig. 3. Normalized contrast response functions averaged across all subjects are shown for all activated areas in Fig. 4A. Responses were normalized by calculating them as fractions of the response evoked by the highest contrast stimulus.

In the LGN and in all visual cortical areas except MT, fMRI responses increased monotonically but nonlinearly as a function of stimulus contrast [main effect of contrast: $P < 0.001$ for all areas; $P < 0.01$ for LGN, V1, V2, V3, V4, V3A; n.s. for MT; interaction of area and contrast: $P < 0.01$ (Figs. 3, 4A)]. In the LGN, responses to stimulus contrast $<10\%$ amounted to $41\%$ of the maximum response. In visual cortex, an even greater sensitivity to low-contrast stimuli was seen. In V1, V2, V3, V4, and V3A, responses to the lowest contrast stimulus tested (4%) evoked 48 to $62\%$ of the maximum response. In area MT, responses were saturated at the lowest contrast level when stimuli were presented in an increasing sequence (Figs. 3, 4A). In the LGN, responses increased gradually with contrast.

**Fig. 2.** Time series of functional magnetic resonance imaging (fMRI) signals in the LGN and visual cortex. Signals obtained in experiment 1 averaged across subjects ($n = 6$) for the right (gray lines) and left (black lines) LGN (A) and visual cortex (B). Signals in visual cortex were averaged across all activated areas. Half of the runs started with checkerboard presentations to the left hemifield (left panel), activating the right LGN and visual cortex; the other half started with presentations to the right hemifield (right panel), reversing the response pattern. Each condition was repeated 3 times during a scanning session.
up to a 50% level above which only small further increases were obtained. In visual cortical areas (except MT), the dynamic range of responses was smaller and near-saturation levels were reached at contrast levels of 35% (Figs. 3, 4A). Contrast response functions (CRFs) for cortical areas were shifted leftward on the contrast axis relative to the LGN CRF (Fig. 4A), suggesting that the LGN had a lower contrast gain than early and intermediate cortical processing stages.

The sensitivity to luminance contrast across the visual system was further probed by computing a contrast modulation index (CMI) for each area and subject. The CMI compares the responses evoked by the minimum and maximum contrast stimuli for each area, providing a measure of sensitivity to low-luminance contrast. High index values indicate poor sensitivity; low index values indicate high sensitivity. The CMIs for LGN and visual cortex averaged across subjects are shown in Fig. 4B. CMIs decreased gradually (with the exception of area MT) and significantly from early to intermediate processing levels (main effect of area: $P < 0.001$), indicating increasing sensitivity to low-luminance contrast in extrastriate cortex (Fig. 4B). In the LGN and V1, contrast sensitivity was significantly lower than that in areas V3, V4, and MT (LGN, V1 vs. V3/VP: $P < 0.05$; LGN, V1 vs. V4: $P < 0.05$; LGN, V1 vs. MT: $P < 0.001$). Area MT showed the highest sensitivity to low contrast with an index value close to 0, which was significantly different from all other visual areas.

Effects of contrast adaptation were investigated by analyzing CRFs obtained during runs of increasing and decreasing contrast presentations separately. We predicted that prolonged viewing of high-contrast stimuli in the decreasing contrast condition may lead to stronger contrast adaptation than during the increasing contrast condition. Such contrast adaptation may result in a reduction of responses to low-luminance contrast (e.g., Ohzawa et al. 1982; Sclar et al. 1989). Figure 4C illustrates CRFs for areas V4 and MT during the 2 presentation conditions. In area V4, there were no significant differences in CRFs obtained during the 2 conditions. Similar results were found in the LGN and in areas V1, V2, V3, and V3A. In area MT, responses were saturated by low-luminance contrast when the stimuli were presented in an increasing sequence. However, responses to low-contrast stimuli were significantly attenuated when stimuli were presented in a decreasing sequence, presumably attributable to stronger contrast adaptation in that condition. Such contrast adaptation appeared to affect contrast gain in area MT but not in other visual areas, suggesting differences in the effects of contrast adaptation across visual areas.

Responses as a function of flicker reversal rate in the LGN and visual cortex

In experiment 3, fMRI signals evoked by stimuli varied in flicker reversal rate were investigated in the LGN and compared with those obtained across visual cortex. Checkerboard stimuli were used that reversed luminance at 3 different rates: 0.5, 7.5, and 20 Hz. Stimulus contrast was held constant at

---

**FIG. 4. Modulation by stimulus contrast: normalized response functions and contrast modulation index. A:** normalized contrast response functions. For each area, responses were plotted as a fraction of the response evoked by the 100% contrast stimulus and averaged across subjects ($n = 6$). In all visual areas except MT, responses increased monotonically with contrast. In MT, responses were saturated at 4% contrast when stimuli were presented at increasing contrast levels. Vertical bars indicate SE calculated across subjects. **B:** contrast modulation index. For each area, a contrast modulation index was calculated to reflect the contrast sensitivity in a given area (see METHODS). Index values decreased gradually from early to intermediate processing stages along the visual pathway, indicating increasing sensitivity to low contrast. Error bars indicate SE calculated across subjects. * $P < 0.05$, significance level as calculated by a t-test comparing index values obtained in each area relative to the values obtained in the LGN and V1. **C:** contrast adaptation effects in V4 and MT. Normalized contrast response functions were averaged across subjects and plotted separately for the different presentation conditions of either increasing or decreasing contrast sequences. Stimsuli presented at decreasing contrast presumably produced stronger contrast adaptation, which may affect contrast gain. Contrast gain was higher in MT during presentations of increasing contrast, relative to decreasing contrast, but was unaffected by presentation order in V4 and the other activated visual areas (not shown). Vertical bars indicate SE calculated across subjects.

---

**FIG. 3. Modulation by stimulus contrast: fMRI signals in LGN, V1, V4, and middle temporal visual area (MT).** Time series of fMRI signals obtained in experiment 2 averaged over all subjects ($n = 6$) and scans. Flickering checkerboard stimuli were presented at various levels of stimulus contrast. Data were combined across left and right hemispheres. In the LGN, V1, and V4, responses increased monotonically with stimulus contrast. In MT, responses were saturated at the lowest contrast tested when stimuli were presented at increasing contrast levels (see also Fig. 6C).
by the checkerboard stimuli in the LGN and in each activated area in Fig. 6, 5. Mean signal changes and normalized response functions. For each area, mean signal changes were normalized to the response evoked by the 20-Hz stimulus and averaged across subjects; the 0.5-Hz stimulus evoked about 80% of the overall signal in the LGN and visual cortical areas other than MT. Vertical bars indicate SE calculated across subjects.

Differences in flicker rate modulated fMRI signals evoked by the checkerboard stimuli in the LGN and in each activated cortical area (main effect of flicker rate; \( P < 0.01 \) for LGN, V1, V3, V3A; \( P < 0.05 \) for V2, V4, MT). In all areas, the 0.5-Hz stimulus evoked a significantly smaller response than the 20-Hz stimulus [0.5 vs. 20 Hz: \( P < 0.05 \) for all areas (Figs. 5, 6)]. However, the response evoked by the 0.5-Hz stimulus was surprisingly strong and totaled about 80% of the response elicited by the 20-Hz stimulus in the LGN and in cortical areas other than MT (Fig. 6B). In MT, the 0.5-Hz stimulus was only 62% (±7% SE) of the response evoked by the 20-Hz stimulus and elicited a significantly smaller response than in the other areas. In the LGN and in V1, the 7.5- and 20-Hz stimuli evoked similar responses that were significantly stronger than the response to the 0.5-Hz stimulus [0.5 vs. 7.5 Hz: \( P < 0.05 \); 7.5 vs. 20 Hz: n.s. (Figs. 5 and 6A)]. In extrastriate areas V4, V3A, and MT, on the other hand, the 0.5- and 7.5-Hz stimuli evoked similar responses that were significantly smaller than those evoked by the 20-Hz stimulus [7.5 vs. 20 Hz: \( P < 0.05 \); 0.5 Hz vs. 7.5 Hz: n.s. (Figs. 7 and 8A)]. The response pattern in areas V2 and V3 was intermediate in the sense that only responses evoked by the 0.5-Hz stimulus and the 20-Hz stimulus differed significantly, whereas responses evoked by the 7.5-Hz stimulus were not significantly different from either one. These results suggest that the LGN and V1 respond most sensitively to changes in flicker rate in the 0.5- to 7.5-Hz range. Extrastriate areas V4, V3A, and MT, on the other hand, appear to respond most sensitively within the frequency range of 7.5 to 20 Hz.

Visually evoked responses in the pulvinar

The pulvinar was not significantly activated in any of the subjects tested in experiments 1–3, in which flickering check-
Checkerboard stimuli were presented in alternation to the right or left hemifield under passive viewing conditions. This negative finding can be interpreted in several different ways. First, activity in the human pulvinar may be strongly modulated by top-down influences such as selective attention (e.g., Robinson and Petersen 1992). Second, areas in the human pulvinar may contain visually responsive neurons with large receptive fields (RFs) extending over the entire visual field. If so, the statistical analysis of experiments 1–3 that compared activations evoked by right versus left hemifield presentations “subtracted out” pulvinar activations. Finally, it is possible that the spatial resolution or sensitivity of fMRI techniques used in the present study were insufficient to reveal activations within the pulvinar in experiments 1–3. Even though it was not possible to test the latter hypothesis with our current fMRI technique, we explored the first 2 possibilities further in experiment 4 by probing activations in the pulvinar during bilateral attended or passively viewed checkerboard presentations and attended unilateral checkerboard presentations to the left or right hemifield. We previously reported attentional modulation found in the LGN with this and other attention paradigms elsewhere (O’Connor et al. 2002). Here, we report functional activations obtained in the pulvinar.

Flickering checkerboard stimuli were presented simultaneously to both hemifields interleaved with blank periods or unilaterally in alternation to the right or left hemifield while subjects maintained fixation. Subjects were instructed by an arrow presented at fixation to direct attention either to the left or right checkerboard and to detect luminance changes that occurred at random times and at 10° eccentricity. Behavioral performance in this task was 88 ± 6% correct with the bilateral presentations and 76 ± 29% correct with the unilateral presentations. During bilateral attended presentations of the checkerboard stimuli 2 regions within the pulvinar were consistently activated across subjects and were found to be located superior and medial to the LGN activations (Table 2; Figs. 7 and 8). The region in the right pulvinar is depicted for individual subjects in Fig. 7A and in Fig. 8, A–C. Mean Talairach coordinates across all subjects were $x = 17$, $y = -24$, $z = 12$ for the activated region in the right pulvinar and $-12, -24, 8$ for the activated region in the left pulvinar. Given the individual variability of the locations of activated regions within the pulvinar, it is not clear whether the regions in the left and right pulvinar represent corresponding visual areas. The mean activated volume was 101 mm³ (±20 SE) for the region in the right pulvinar and 95 mm³ (±8 SE) for the region in the left pulvinar, averaged across all subjects and experiments (Table 2). The time series of fMRI signals in the regions of the left and right pulvinar were averaged across subjects and are shown in Fig. 8D. The time series were clearly linked to the 4 blocks of attended visual presentations; mean fMRI responses were 0.72% signal change (±0.03 SE) in the left pulvinar and 0.67% signal change (±0.03 SE) in the right pulvinar. When subjects directed attention to checkerboard stimuli presented unilaterally in alternation to the right and left hemifield, no activations in the pulvinar were found (Fig. 7B), supporting the hypothesis that visually responsive neurons in the activated region of the pulvinar had large RFs extending over the entire visual field. Finally, to further test the possibility that the visually evoked pulvinar activity was strongly modulated by selective attention we performed a control experiment in which subjects did not direct attention to the bilaterally presented checkerboard stimuli, but rather passively viewed the stimuli while maintaining fixation. Indeed, in support of our hypothesis, no activation in the pulvinar was found under these conditions, as illustrated in Fig. 7C.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Right</th>
<th>Left</th>
<th>Volume, mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
</tr>
<tr>
<td>S1</td>
<td>23</td>
<td>-29</td>
<td>10</td>
</tr>
<tr>
<td>S2</td>
<td>13</td>
<td>-24</td>
<td>10</td>
</tr>
<tr>
<td>S3</td>
<td>13</td>
<td>-19</td>
<td>14</td>
</tr>
<tr>
<td>S5</td>
<td>18</td>
<td>-23</td>
<td>15</td>
</tr>
<tr>
<td>Average</td>
<td>17</td>
<td>-24</td>
<td>12</td>
</tr>
</tbody>
</table>

$S =$ subject.

FIG. 8. Functional activation and time series of fMRI signals in the pulvinar. A–C: individual results from 3 subjects tested in experiment 4 showing a consistently activated region in the right pulvinar (see also Table 2). Flickering checkerboard stimuli of high contrast were presented simultaneously to both hemifields in blocks of 16 s interleaved with equally long blank periods. Subjects were instructed to direct attention to the right or left checkerboard stimulus and to detect a luminance change occurring randomly in time along the checkerboard arc at 10° eccentricity. Time series of fMRI signals in activated regions of the left and right pulvinar averaged across subjects ($n = 4$) clearly reflect the 4 blocks of attended presentations within a given scan. Other conventions as in Fig. 1.

TABLE 2. Pulvinar: Talairach coordinates and activated volumes

*J Neurophysiol • VOL 91 • JANUARY 2004 • www.jn.org*
DISCUSSION

Using fMRI at 3 T, we investigated the functional anatomy and basic response properties of the human LGN and attention-related activity in the human pulvinar. Flickering checkerboard stimuli presented in alternation to the right or left hemifield reliably activated the LGN, confirming previous studies that demonstrated LGN activation at 4 T (Chen and Zhu 2001; Chen et al. 1998a,b, 1999). The LGN is unique in that its location can be identified both on the basis of anatomical–structural and functional data. A comparison of these different location measures in normalized space provides an estimate of the topographic precision of hemodynamic signals relative to their underlying neural source. With an in-plane voxel resolution of about $3 \times 3$ mm$^2$, the average peak of the functional activations was found to be within ±2 mm of the anatomical location of the LGN, indicating excellent topographic specificity of fMRI signals. The mean activated functional volumes of 244 mm$^3$ for the right LGN and 234 mm$^3$ for the left LGN are similar to those reported by Chen et al. (1998a) using similar scanning parameters at 4 T. Because of the coarse spatial resolution of our functional imaging technique, however, functional activations appear to overestimate LGN volumes. Anatomical LGN volumes, as determined in histology studies, have been reported to range from 66 to 157 mm$^3$ in the human brain (Andrews et al. 1997; Putnam 1926; Zworykin 1980, 1981). Amplitudes of visually evoked fMRI signals were found to be considerably lower in the thalamus than in cortical areas. However, thalamic fMRI signals were found to be sufficiently robust to study contrast and flicker rate response functions in the LGN and to compare them to those obtained in visual cortex.

In all visual areas except MT, responses increased monotonically as a function of stimulus contrast, confirming previous single-cell physiology and neuroimaging studies (Albrecht and Hamilton 1982; Avidan et al. 2002; Boynton et al. 1996; Carandini et al. 1997; Cheng et al. 1994; Dean 1981; Logothetis et al. 2001; Sclar et al. 1990; Tolhurst et al. 1981; Tootell et al. 1995). In the LGN, populations of neurons with different contrast sensitivities contributed to the collective responses measured with fMRI. Single-cell recording studies have shown that parvocellular (P) cells are typically not responsive to contrast stimuli lower than 10% and have a 10-fold lower contrast gain than that of magnocellular (M) cells, which typically respond to contrast stimuli as low as 2% (Lee et al. 1989; Sclar 1990; Shapley et al. 1981). The spatial resolution of our imaging techniques did not permit a dissociation of the parvocellular and magnocellular parts of the LGN. However, the contrast sensitivity of the M-pathway can be indirectly estimated from the population response of area MT, which receives a dominant input from the magnocellular stream, as evidenced by anatomical and lesion studies (e.g., Lund et al. 1976; Maunsell and Van Essen 1983; Maunsell et al. 1990). Single-cell physiology studies have shown that contrast sensitivities of neurons in MT and in M-LGN are similar, with average semisaturation of responses about or slightly below 10% contrast in M-LGN neurons and in MT neurons, respectively (Sclar 1990). The results from the present study and a previous imaging study (Tootell et al. 1995) demonstrate response saturation in human MT with contrast stimuli as low as 4%, suggesting high contrast sensitivity for the magnocellular stream in the human visual system. Therefore the relatively small LGN responses in the low-contrast range (<10%) may be attributed to a dominant influence from P cells, which outnumber M cells several times in the LGN (Andrews et al. 1997; Dreher et al. 1976; Perry et al. 1984).

Responses of the LGN as a function of stimulus contrast differed in several respects from CRFs obtained in visual cortex. First, responses in the LGN were evoked by a wider range of contrast stimuli; that is, the dynamic range of the CRF was larger. In cortical areas, CRFs were steeper and saturated more readily, thereby reducing the dynamic range of the contrast functions. These results are in agreement with single-cell physiology studies (Sclar 1990) and suggest that neural populations in the LGN can provide information about changes in contrast over a wider range than in cortex. Second, the contrast gain in LGN was lower than that in cortical areas, as indicated by a steeper slope and a leftward shift of cortical CRFs along the contrast axis. In inactivation studies, it has been shown that cooling of V1 leads to decreases of contrast gain in LGN neurons, suggesting that contrast gain in the LGN is controlled by cortical mechanisms that are mediated by corticofugal pathways (Przybyszewski et al. 2000). Finally, LGN and V1 were significantly less sensitive to low luminance contrast than extrastriate cortex. A gradual increase of sensitivity to low-luminance contrast was obtained from early to intermediate processing levels of the visual system (see also Avidan et al. 2002). These differences in contrast sensitivity may be attributed to the increasing receptive field size of neurons across visual cortex. For example, a neuron in area MT may receive inputs from as many as 10,000 M-cells, which would increase its contrast sensitivity resulting from summation of inputs (Sclar 1990). Similarly, the larger contrast sensitivity of M-cells relative to that of P-cells has been attributed to the larger receptive field sizes of M-cells (Lennie et al. 1990).

Converging evidence from single-cell physiology studies in monkeys and functional brain-mapping studies in humans suggest that neural responses in visual cortex and in the LGN can be modulated by top-down processes such as attention (e.g., Desimone and Duncan 1995; Kastner and Ungerleider 2000; O’Connor et al. 2002). Such attentional response modulation has been shown to affect neural responses in extrastriate cortex more strongly than in early visual cortex. Therefore it is important to consider that our evaluation of contrast sensitivity was compromised by attentional modulation of neural activity in the visual system. Moreover, selective attention directed to contrast-modulated stimuli has been shown to affect responses to low-contrast stimuli more strongly than those to high-contrast stimuli (Reynolds et al. 2000). Because of the interaction of stimulus contrast and attention it is not clear whether there is an ideal paradigm to measure contrast response functions in awake subjects. The use of passive fixation conditions in the present study appeared to be a reasonable compromise. If the decrease in the contrast modulation index in extrastriate cortex reflected stronger attentional modulation of visually evoked responses, rather than increasing contrast sensitivity, the results for the LGN would be difficult to explain. We recently showed that responses in the human LGN can be modulated by selective attention (O’Connor et al. 2002). Moreover, attentional effects in the LGN were stronger than in V1 and on the order of those obtained in V4 and MT. Thus if the CMI reflected attentional modulation, one would expect the LGN index to be
smaller than the V1 index and on the same order as the indexes obtained in V4 and MT. Instead, we found that the CMI was similar in the LGN and V1, decreased systematically in extrastriate cortex except MT, and was close to zero in MT. These findings are in better agreement with the interpretation that differences in the contrast modulation index are attributed to increasing RF sizes in extrastriate cortex and a predominant magnocellular input to area MT. Although we cannot entirely rule out the possibility of attentional influences on our contrast response functions, we believe that the current results are a good estimate for such functions in awake and generally attentive subjects.

In the LGN and V1, maximum responses were evoked with flicker reversal rates of 7.5 Hz with little additional response increases above that frequency, in agreement with previous functional brain-imaging studies demonstrating peak responses evoked by stimuli flickering at 8 Hz in V1 (Fox et al. 1986; Kwong et al. 1992). In addition, peak responses evoked by stimuli flickering at 20 Hz were found in extrastriate areas V4, V3A, and MT, confirming previous findings of an fMRI study that used drifting gratings varied in temporal frequency (Singh et al. 2000).

In previous single-cell physiology studies, drifting sine-wave gratings have typically been used to characterize neural responses as a function of temporal changes. With these stimuli, the rate of alternations of entire ON-OFF cycles, or periods of the sine wave, defines temporal frequency. In the present study, ON-OFF reversals rather than cycles defined the flicker rate of the checkerboards. Consequently, we will compare our results to those obtained with drifting sine-wave gratings at temporal frequencies of 0.25, 3.75, and 10 Hz that correspond to our flicker rates of 0.5, 7.5, and 20 Hz. In the macaque monkey, P-LGN neurons have been found to respond most to stimuli at temporal frequencies close to 10 Hz, and M-LGN neurons to stimuli at frequencies close to 20 Hz (Derrington et al. 1984; Hicks et al. 1983; Merigan and Maunsell 1990, 1993). Further, it was shown that P cells still responded to stimuli lower than 1 Hz, whereas such stimuli did not evoke responses in M cells (Hicks et al. 1983). Our results suggest that LGN responses evoked by the lowest-frequency stimulus may be attributed to a predominant parvocellular influence. The low spatial frequency of the checkerboard stimulus presumably favored the activation of P cells, which, unlike M cells, do not show response attenuation at low spatial frequency (Enroth-Cugell et al. 1983; Hicks et al. 1983). In area MT, the relatively small responses evoked by the lowest-frequency stimulus and the response preference in the high-frequency range are consistent with the notion that this area receives a dominant magnocellular input. Neurons in areas V1, V2, and V3 have been shown to respond optimally to temporal frequencies between 3 and 6 Hz (Foster et al. 1985; Gegenfurtner et al. 1997; Levitt et al. 1994). Despite significant differences in visual stimuli and methods to estimate neural activity, our finding of peak responses at temporal frequencies around 4 Hz (7.5-Hz reversal rate) in these early cortical areas is in remarkable agreement with the results from single-cell physiology.

Finally, our results can also be related to psychophysical data. At spatial frequencies around 1 cycle/deg, contrast-detection curves peak at temporal frequencies of about 3 Hz (Kelly 1979). Thus neural responses in the LGN and V1 with peak sensitivity around 4 Hz might predict psychophysical temporal frequency functions better than neural responses in extrastriate cortex with peak sensitivity at higher frequencies. However, studies using a combination of fMRI and psychophysics in the same subjects will be needed to test this idea further.

With the experimental designs used to study response properties of the LGN, we found no activations in the human pulvinar. However, regions in the dorsomedial right and left pulvinar were found to be consistently activated when flickering checkerboards were presented bilaterally and subjects directed attention to the stimuli, but not when subjects passively viewed them or when the stimuli were attended but presented unilaterally. These results suggest that, first, regions in the dorsomedial pulvinar were strongly modulated by selective attention, and that, second, these regions contained neurons with large RFs extending across the entire visual field. Eye movements were carefully controlled in these experiments, ruling out the possibility that systematic deviations from fixation confounded the attentional modulation (see O’Connor et al. 2002; Fig. 5).

It has been shown in the macaque monkey that the pulvinar contains in its inferior, lateral, and medial subdivisions at least 4 visual areas that can be distinguished on the basis of their visuotopic organization and connectivity with cortical visual areas. Two of these areas are located in the inferior and lateral part of the pulvinar (Ungerleider et al. 1984). These areas contain clearly organized retinotopic maps and are connected with cortical areas V1, V2, V4, and MT (Adams et al. 2000; Maunsell and Van Essen 1983; Ungerleider et al. 1983). A third area, described on the basis of its connections with area MT (Ungerleider et al. 1984), is located in the medial portion of the inferior subdivision and does not appear to have a well-defined retinotopic map. A fourth area, known as Pdm, has been identified dorsal to these areas and also does not show much visuotopic organization. Importantly, neural responses in Pdm were related to visuospatial attention (Petersen et al. 1985; Robinson et al. 1986). It was shown in particular that neural responses in Pdm were enhanced when an animal attended to a visual stimulus compared with when the same stimulus was ignored (Petersen et al. 1985).

Several of our findings support the idea that the activated regions in the left and right dorsomedial pulvinar may be homologous to area Pdm of the macaque pulvinar. First, the human pulvinar areas were strongly modulated by visuospatial attention. Such attentional modulation has been described for Pdm, but not for other visual areas of the macaque pulvinar (Petersen et al. 1985). Second, the human pulvinar areas appeared to have a coarse visuotopic organization with large receptive fields (RFs) extending over the entire visual field. Neurons with large RFs of >30° extending across the vertical meridian have been found in macaque Pdm, but not in other pulvinar areas (Petersen et al. 1985). Finally, it is unlikely that the human pulvinar activations occurred in retinotopically organized pulvinar areas because they were not seen in experiments 1–3. It is not clear why retinotopically organized areas of the human pulvinar were not activated in our studies. However, given the small size of the activated volumes within the pulvinar, this may reflect a lack of sensitivity and spatial resolution of the fMRI methods used here. Therefore further studies using high-resolution fMRI will be needed to confirm and extend the preliminary results reported here. Interestingly, activations in the human pulvinar have been demonstrated during
visual imagery (Chen et al. 1998b). However, these activations were found in lateral and inferior rather than in dorsomedial parts of the pulvinar. Thus it is possible that the human pulvinar contains several visual areas that can be modulated by top-down processes.

Several lines of evidence indicate that the pulvinar is part of a distributed network subserving visuospatial attention (Kastner and Ungerleider 2000). First, when the pulvinar is inactivated by muscimol, monkeys show impairments in filtering out irrelevant information from distracter stimuli (Desimone et al. 1990). A similar role of the pulvinar in filtering unwanted information has also been suggested by neuroimaging studies in humans (LaBerge and Buchsbaum 1990). Second, patients with lesions in the pulvinar exhibit visuospatial hemineglect, an impairment in directing attention to the contralateral hemifield (Karnath et al. 2002; Rafal and Posner 1987). Importantly, the lesion sites of neglect patients have been located in the dorsomedial pulvinar. The attention-related activity in dorsomedial regions of the human pulvinar of the present study was located in the same region of Talairach space as the lesion site in neglect patients (Karnath et al. 2002). Taken together, our findings support the notion of a functional role of the pulvinar in visuospatial attention.

In our previous work, we showed that responses in the human LGN are modulated more strongly by selective attention than those in primary visual cortex (O’Connor et al. 2002). This finding suggested that attentional modulation in the LGN may not only be attributed to feedback from V1 but may also be mediated by additional feedback sources such as the thalamic reticular nucleus or the superior colliculus. However, an alternative interpretation of this finding was that attention-related pulvinar activity accounted for the larger attentional modulation in the LGN because it was not possible to spatially resolve activity evoked in the LGN and in the pulvinar using fMRI. Here we have shown that attention-related activations in the pulvinar were clearly distinct from LGN activations and that the latter interpretation is therefore unlikely.

Acknowledgments
We thank D. M. Beck and K. A. Schneider for valuable discussions. Present addresses: M. M. Fukui, Department of Psychology, New York University, New York, NY 10003; U. Herwig, Psychiatric University Hospital, Geriatric Psychiatry Unit Hegibach, Minervastr. 145, 8032 Zurich, Switzerland.

Grants
This study was supported by National Institute of Mental Health Grants RO1 MH-64043 and P50 MH-62196 and the Whitehall Foundation to S. Kastner and by National Science Foundation Graduate Research Fellowships to D. H. O’Connor and M. A. Pinski.

References