Spatially Distributed Encoding of Covert Attentional Shifts in Human Thalamus

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INTRODUCTION

From a neural perspective, spatial visual attention is an integrated ability of the brain to coordinate the allocation of processing resources across multiple cortical areas to the location of greatest behavioral significance (Beck and Kastner 2009; Duncan 2006; Duncan et al. 1997; Shipp 2004). Top-down attention is thought to be mediated by a control signal originating from a fronto-parietal cortical network interacting with visual processing along the occipito-temporal pathway (Corbetta and Shulman 2002; Kastner and Ungerleider 2000; Moore 2006; Yantis and Serences 2003). As these two cortical networks connect with largely separate zones within the thalamus (Selemon and Goldman-Rakic 1988; Shipp 2003), our thesis is that the engagement of thalamic nuclei with attention might divide into similarly discrete, binary categories—i.e., as a source or sink for attentional functionality. Recent progress in imaging thalamic correlates of covert visual attention has focused on the latter effect in visual nuclei, showing attentional enhancement of the response of the inferior pulvinar, and lateral geniculate nucleus (LGN), to contralaterally presented stimuli (Cotton and Smith 2007; O’Connor et al. 2002; Schneider and Kastner 2009; Smith et al. 2009a). By contrast, we set out to examine spatial tuning in the pan-thalamic pattern of activation induced by cued shifts of attention to parafoveal targets, addressing mechanisms of top-down control rather than the modulation of visual processing.

Neuropsychological studies certainly link thalamic damage to various forms of attentional disturbance, such as contralateral neglect (Karnath et al. 2002; Kaufman et al. 2009; Ortigue et al. 2001) or deficits in covert attention (Arend et al. 2008; Rafal and Posner 1987; Ward and Arend 2007) or filtering distracters (Snow et al. 2009). However, the thalamic lesions are rarely sufficiently focal to draw precise subthalamic (i.e., nuclear) functional inferences. Although there is a wealth of imaging studies documenting cerebral correlates of covert attention, this work has produced surprisingly meager evidence of any contribution from the thalamus. A common problem—at least in respect of thalamic observations—is the use of pooled-subject group analysis: the size of individual thalamic nuclei is comparable to the magnitude of the local spatial transformations achieving stereotaxic normalization, such that there is little guarantee that equivalent thalamic activations (or nuclei) will be successfully coregistered. This may explain the absence of thalamic activation in studies of covert attention that do, nonetheless, report subcortical activity in cerebellum and/or putamen (Corbetta et al. 1998; Hopfinger et al. 2000; Nobre et al. 2000; Perry and Zeki 2000). In studies that report only cortical activation, it is not always clear whether subcortical activation was absent, excluded from regions of interest, or simply went unreported (Corbetta et al. 2000; Ikai and Curtis 2008; Kelley et al. 2008; Serences and Yantis 2007). Three studies, to our knowledge, have reported thalamic loci linked to the operation of covert attention: these are all unilateral, variously attributed to right ventrolateral nucleus (Gitelman et al. 1999), left anterior thalamus and left pulvinar (Yantis et al. 2002), and left ventroposteromedial nucleus1 (de Haan et al. 2008).

Our source data were obtained in an event-related functional MRI (fMRI) study of stimulus reportability (Hulme et al. 2009), where three subjects viewed a briefly presented, circular array of disc stimuli surrounding fixation and reported the presence or absence of a disc at a specified location. The cue followed the offset of the disc targets, requiring subjects to perform detection based on their visual iconic memory (Geigenfurter and Sperling 1993). The angular spacing of the discs was commensurate with the limit of attentional resolution, the minimum interobject separation at which two objects can be individuated (Intriligator and Cavanagh 2001). By

1 The thalamic locus specified by the given coordinates is from the interactive atlas at www.neurovia.umn.edu/cgi-bin/tal_atlas.
contrast, previous imaging studies of covert attention have commonly used just two targets, located in opposite hemifields. The one previous study requiring readout from iconic memory concluded that the spatial attention task activated similar cortical networks independent of providing the cue before or after the stimulus (Ruff et al. 2007). To maximize the sensitivity of statistical inference, we collected a high volume of single-subject data and restricted the analysis to a bilateral perithalamic region. We sought to identify thalamic nuclei not by stereotaxic coordinates but by cross-referencing individual anatomic criteria from nontransformed brain images to a standard thalamic atlas (Morel et al. 1997). Compilation of active sites across subjects and hemispheres highlighted thalamic nuclei linked to the cortico-thalamocortical circuitry of the frontoparietal network and also to thalamo-striatal circuitry. Interpretation of this pattern of activation follows the rationale outlined by visuomotor theories for the origins of covert attention (Awh et al. 2006; Moore et al. 2003).

METHODS

Subjects, stimuli, and task

Three highly experienced psychophysical observers, naïve to the aims of the experiment (2 males and 1 female; age, 21–25 yr; all right handed and with normal vision) were scanned. The inclusion criterion for all subjects was an ability to maintain consistently stable fixation for the duration of each session (1 subject excluded on this basis). All subjects gave informed consent in accordance with the Declaration of Helsinki, and the Ethics Committee of the National Hospital for Neurology and Neurosurgery, London, UK, granted ethics approval for the study. We used a case study design because the degrees of freedom were more powerfully deployed within subjects to maximize sensitivity for detecting small spatial maps. Accordingly, we acquired a large amount of data from each subject (>5,000 volumes/subject).

The stimulus consisted of eight small discs (solid circular shapes of diameter 0.5°), displayed at 3° eccentricity from fixation (with 1 disc per octant) undergoing a sinusoidal luminance transient on a uniform gray background (98 Cd/m²). Sinusoidal luminance transients were chosen because they minimized visual afterimages as tested psychophysically and also because they increased the saliency of the discs such that subjective indices of perceptual salience (2-alternative forced-choice comparative salience judgment) and objective measures of detection accuracy (d-prime > 3.5) were higher than for a simple ON-OFF transient of the same contrast and duration.

The task was a variant of the Sperling “partial report” paradigm (Gegenfurtner and Sperling 1993). Each trial started with the onset of the disc array transient, which was presented for 200 ms and followed, after a variable delay (200, 1,000, or 2,000 ms), by a cue (100 ms) pointing to 1 of the 16 positions. The cue itself was a thin black line, extending radially from the center of the fixation cross to a point at 1° eccentricity in the direction of one pseudorandomly selected position. Subjects were instructed to indicate in a two-alternative, forced-choice judgment whether the disc at the cued location had been present or absent by pressing one of the two buttons on a response box. If saccades were detected during the trial, scanning sessions were stopped and restarted with verbal feedback issued to the subject (instantiated once only, for subject H.E.). The circular arrangement and equal luminance of the discs minimized the likelihood of inducing reflexive saccades.

Subjects were trained extensively before scanning, with two aims: 1) to find the contrast parameters of the luminance transients for each subject that would result in performance within a controlled range (92.5–97.5% for short delay trials) and 2) to ensure performance had stabilized and that no further learning was taking place (see Supplementary Procedures for additional details).

Scanning and image processing

Scanning was performed on a 3-T Siemens Allegra fMRI scanner using standard scanning protocols (TR = 2.47/TE = 65 ms) with a native resolution of 2 mm isotropic voxels. There were 10 separate sessions per subject, each consisting of an average of 730 volumes (~30 min/session). The first five images of each run were discarded to allow for magnetic saturation effects. Neither phase mapping nor unwarping was necessary in view of the fact that the thalamus occupies a relatively well-shimmed region, with little susceptibility-related echo-planar imaging artifact.

The remaining images were realigned, resliced, and coregistered to the individual subjects’ structural scans. The data were analyzed using a voxel-wise general linear model as implemented in SPM2 software (Wellcome Trust Centre for Neuroimaging, London, UK). The echo

FIG. 1. Spatial and temporal configuration of the stimulus display. Eight target discs, diameter 0.5°, distributed among 16 invariant positions at 3° eccentricity from fixation (with 1 disc per octant) underwent a sinusoidal luminance transient of 200 ms duration. The cue, a short line pointing from fixation to 1 position, was presented for 100 ms after a further variable interval. Subjects indicated the presence or absence of a disc at the cued location from iconic memory.

2 The online version of this article contains supplemental data.
planar-imaging images were realigned spatially and filtered temporally with a band-pass filter with a low-frequency cut-off period of 128 s. Global changes in activity were removed by proportional scaling. To maximize correspondence of thalamic landmarks in the T1-weighted structural images across subjects, standard stereotaxic normalization (i.e., with respect to Talairach/MNI coordinates) was omitted in favor of a manual registration procedure. The latter corrected small variations in pitch of the body of the thalamus with respect to the standard AC-PC plane (requiring rotations <5°). The first functional volume (of the 1st session for each subject) was coregistered to the manually adjusted structural before automatic realignment of the remaining functional volumes. Once realigned, all functional and the structural were cropped down to dual (i.e., left and right) perithalamic regions, symmetrical about the midline (each 3.7 × 3.7 × 3.7 cm, fully enveloping the thalamus of a single hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere). The functional images were supersampled to yield 1 mm cubic voxels; the smoothness introduced by this reslicing (performed hemisphere).

Stimulus onsets and attentional shifts were modeled as events time-locked to their occurrence (respectively the onset of the disc array and of the cue). Standard multiple linear regression protocols were used to estimate the parameters of the BOLD response to the varying spatial configurations of stimuli and cue. To characterize the spatial selectivity of activation mediated by attention, we explored the main effect of cue direction (relative to implicit baseline) in respect of single positions, octants (2 of 16 positions), quadrants (4 of 16), and superior/inferior and right/left hemifields (8 of 16 positions). A separate set of contrasts examined the main effect of stimulus onset at specific locations (exploiting the fact that the presence of a disc at the specified position in 50% of trials was not correlated with the position of any other disc in the 7 remaining octants). All other factors relating to decision and report elements of the task were modeled as effects of no interest, because the balanced design of trial delivery eliminated any correlation with cue direction. The factor of cue delay was treated similarly. The reason cues were presented with variable delays was to prevent strong temporal expectations for their arrival; as expected, longer delays induced more error in target detection. However, because attentional orientation and not target detection was the focus of this study, we maximized statistical power by pooling trials across cue delay and, as noted, irrespective of target presence/absence and correct/incorrect responses. A similar analysis in respect of cue direction was performed on the control data (in which subjects observed the same visual stimulus without performing the task). Note that the control conditions were not part of the factorial design of the experiment; they were implemented in separate sessions (to serve as a localizer), and therefore, the control data are not used for direct contrast with the task performance data.

The main effects of attentional shifts to separate single positions were jointly rendered onto structural images to show voxel-wise attentional field maps. We present data relating to 6/16 positions (shown as paired sets of 3 equally spaced positions, 1 set rotated by 1 position with respect to the other). We adopted this approach in view of the multiple-position sensitivity of single voxels that precluded use of a conventional 8- or 16-point color wheel method of illustration (because the color wheel assigns a single color/direction to each voxel and thus obscures any more complex spatial response profile). All effects shown are significant at $P < 0.05$ familywise error (FWE-corrected over the peri-thalamic volume).

Fitting functions to the voxel selectivity profiles

We further aimed to determine what function would best characterize the activation of a voxel by the 16 separate directions of attentional shift [the attentional selectivity profile (ASP)]. This is analogous to fitting a tuning curve to the directionally tuned responses of a single neuron but, unlike classical tuning curves, we found that thalamic voxels show complex, multiply peaked profiles (Fig. 5). To quantify such a spatial tuning profile, we fit a function with zero, one, two, three, or four modes to each ASP. We used gradient descent on the posterior probability, with checks for convergence and for replicability. The zero mode function was a flat line, and the peaked profiles consisted of mixtures of between one and four Von Mises functions (the circular analog of a Gaussian and thus suitable for radial position). We selected the fitted function under which the data had the highest likelihood, according to the Bayesian information criterion (BIC) approximation. Note that, although there are a small number of data points, use of the BIC for model selection penalizes the number of parameters, guarding against overfitting; see Supplementary Procedures for a full description.

Thalamic profiling: Anatomical identification of active nuclei

Individual neural activation was specified by reference to the stereotactic atlas of the human thalamus of Morel et al. (1997). The atlas shows series of sections in each of the three cardinal axes, with the sagittal and horizontal series being derived from opposite hemispheres of the same brain. To compare images to atlas sections, we made manual adjustments (<5°) to the horizontal image plane in each subject matching the pitch of the body of the thalamus to the standard AC-PC plane at horizontal level zero. We identified homologous anatomical landmarks to serve as reference points for defining corresponding slices between the atlas and each subject, allowing independent linear scaling in each axis of brain space. The atlas shows a horizontal series of 16 sections from $-1.8$ to $+11.7$ mm with respect to the AC-PC plane; having matched the upper and lower bounding sections, our perithalamic image volume was found to extend a little further ventral, providing two additional levels. A similar procedure was applied to the sagittal series, matching the 18 atlas sections from 3.6 to 19.4 mm lateral to the midline, plus three additional levels more laterally.

The major limitation in the accuracy of the atlas comparison is imposed by interindividual variation in the size and shape of thalamic nuclei, compounded by gross differences in overall thalamic dimensions as shown in Fig. 2 (for another example, see Fig. S9, Supplementary Data/Discussion Section 3A). To improve the registration between fMR images and atlas templates, we routinely distorted the latter to match the outline of the thalamus in each of our subjects; an example is presented in Fig. 3. The ventricular surface of the thalamus is easily discernible, and the reticular nucleus in the atlas templates was fitted to the gray/white interface between thalamus and internal capsule. Internal landmarks that assisted fine tuning of the subjective fit were the habenular nucleus in horizontal sections and the mammillothalamic tract in sagittal sections. The reliability of the resulting match between internal nuclei and template nuclear boundaries will depend on the degree to which nuclear dimensions are proportional to overall thalamic dimensions—a property that has been ascertained previously, at least in the rostro-caudal dimension (Brierley and Beck 1959).

The patterns of activation elicited by 6/16 test positions were superimposed, defining clusters of active voxels responsive (at $P < 0.05$ FWE) to 1 or more of these 6 positions. Most clusters passed a conjunction test (Friston et al. 2005), containing either individual, or contiguous, supersampled voxels activated at more than one single-position contrast. Clusters responsive to a single position alone, and with fewer than eight voxels were disregarded, as a precaution against inferring activation from noise. The surviving single-position clusters were double this size at minimum, with dimensions exceeding two voxels in all axes (i.e., both within and orthogonal to the plane of inspection), ensuring that the same set of clusters would be scored independent of the plane used. Clusters were scored to thalamic nuclei identified by the distorted atlas template at a matching level. Larger voxel clusters frequently overlap one or more nuclear boundaries, and
metric fraction was estimated by the product because we did not analyze data in the coronal plane, the volumetric fraction of active tissue within each nucleus; however, three planes of view, would provide a rough estimate of the clusters, the product of this proportion, obtained separately for all at least one stimulus position. Given roughly spherical voxel nucleus appears in the atlas and the proportion showing activation by the covert task—several nuclei and subject to give a qualitative ranking of the likelihood that each thalamic nucleus is activated by the covert task—several nuclei (et al. 2000).

The results were compiled across anatomical plane, hemisphere, and subject to give a qualitative ranking of the likelihood that each thalamic nucleus is activated by the covert task—several nuclei achieving the maximum score of 6 (i.e., activation noted for at least 1 atlas level in both planes of view, in both hemispheres of all 3 subjects). The next highest score, 5.5, indicates that activation was achieving the maximum score of 6 (i.e., activation noted for at least 1 atlas level in both planes of view, in both hemispheres of all 3 subjects). The next highest score, 5.5, indicates that activation was uniformly scored for that nucleus apart from one plane of view, in one hemisphere, of one subject—and so on. To attempt a more quantitatively satisfying solution, we also recorded the number of levels at which each nucleus appears in the atlas and the proportion showing activation by at least one stimulus position. Given roughly spherical voxel clusters, the product of this proportion, obtained separately for all three planes of view, would provide a rough estimate of the volumetric fraction of active tissue within each nucleus; however, because we did not analyze data in the coronal plane, the volumetric fraction was estimated by the product \((sh)^{1.5}\) (where \(s\) and \(h\) = proportion of active levels in the sagittal and horizontal planes respectively).

**Spatial representation**

**RESULTS**

Spatial representation

Given a native anatomical resolution of 2 mm (i.e., voxels of \(2 \times 2 \times 2\) mm before supersampling), we did not expect our data to evince frank retinotopy. Even in the larger nuclei (e.g., pulvinar or mediodorsal), a spatial map could only span 10–12 mm at most, and individual voxels would comprise relatively large components of it (in comparison to a larger scale cortical map, e.g., V1). We therefore looked, initially, for any evidence of broad spatial tuning, performing contrasts to test for the main effect of attending to different hemifields [upper field positions (13–4) vs. lower field (5–12)] or [left (9–16) vs. right (1–8)] (refer to Fig. 1 for stimulus disc positions). Such contrasts were virtually devoid of activation and gave no significant effects in any subject, even at low thresholds \((P < 0.01\) uncorrected). Next, we performed contrasts at successively narrower sectors of arc, namely quadrants, octants, and single (1/16th) positions (presented in detail below). These showed a clear progression in their outcome, the narrower contrasts producing wider distributions of activation across multiple thalamic sites, in all three subjects, with progressively higher levels of significance. This suggests that attentional representation in the pulvinar, mediodorsal, and other nuclei has a fine angular granularity and that the main effects of the coarser contrasts, indexing attentional shifts to quadrants or hemi-fields, are attenuated by averaging over positions with suboptimal BOLD responses.
It should be noted that this is an attentional effect and not a visual (stimulus-driven) response, on the basis of two additional sets of analyses. First we performed equivalent contrasts at the single position level to test for visual responses to the disc stimuli (note that, although 8 discs were always simultaneously presented, the stochastic nature of the stimulation can allow position-specific visual responses to be recovered; Hulme et al. 2009). Second, we replicated the contrasts for the main effect of cue direction for single positions, octants, quadrants, and hemifields in the control data (where subjects saw the same stimuli but did not perform the task). All such contrasts failed to show significant disc or cue stimulus driven activity in the thalamic region of interest (even at the liberal threshold of $P/0.01$ uncorrected). The absence of a detectable visual response, even from LGN and pulvinar, is not so unexpected, given that our task design (using minimal, short-duration visual transients) was not specifically optimized for visual activation, in contrast to previous positive observations of thalamic visual activity (Cotton and Smith 2007; O’Connor et al. 2002; Schneider and Kastner 2009; Smith et al. 2009a).

The thalamic box region-of-interest included certain extrathalamic components, including brain stem and minor parts of basal ganglia adjoining the internal capsule. These were mainly inactive, containing sporadic activated voxels or small clusters ($P < 0.05$ FWE) in the single position contrasts for attentional shifts. An exception, noted in just one subject (HE), was a swathe of activation extending through bilateral superior colliculus, pretectum, and midline brain stem structures ventral to the thalamus.

**Examination of single-position responses**

Having established that voxels, supersampled at $1 \times 1 \times 1$ mm, had reliable main effects of attention to single positions of our test stimulus, we sought to characterize the nature of their spatial representation. For clarity of visual inspection and presentation, the analysis of topography was restricted to a sample of six test positions, as shown in Fig. 4. Each image shows, superimposed, the main effect ($P/0.05$ FWE) of activations elicited by three separate test positions, as rendered on sagittal slices of the structural MRI from each subject and using the color mixing scheme shown in the key. Two images are shown for each anatomical level, the sample of three evenly spaced positions shown in one image being rotated by one position to give the trio shown in the other image of each pair. The full horizontal and sagittal series are provided in Supplementary Figs. S1–S4. The data afford two general properties: 1) concordance between the overall pattern of response, across the thalamus, to adjacent positions, and 2) single voxels that respond to two or more nonadjacent test positions.
Across the thalamus as a whole, there was variable expression of topography in spatial representation. One notable example occurred in a large cluster of activity located in the dorsal sector of the left posterior thalamus in two subjects (shown in the upper elements of Fig. 4)—a location within the medial pulvinar and adjacent lateral posterior nuclei (see Fig. 317x110 B). We shall refer to this cluster as the “dorsal pulvinar cluster” (DPC). The DPC shows separate but overlapping subzones activated by the red, green, and blue positions (the inset in Fig. 317x77 A shows 1 DPC example with separate color mapping for greater clarity). However, in rotating the sampling by just one position, each zone partially shifts its territory within the dorsal pulvinar cluster.

FIG. 4. Positional specificity of thalamic activation. A: serial sagittal slices displaying position specific BOLD activity superimposed on structural images from 2 individual subjects: W.Y. and H.E. The dials P1 and P2 show the 2 trios of test positions (red, green, and blue), P2 being rotated 1 position clockwise from P1. Red, green, and blue voxels indicate significant effects of an attentional shift to 1 of these 3 positions. The color-mixing scheme shows how voxels responsive to 2 positions are represented by duller yellow, magenta, and cyan hues, whereas responses to all 3 are rendered in black. Each set of 6 images shows P1 and P2 activity in duplicate sections at 3 levels, the corresponding level of the Morel atlas being indicated to the top right of the P2 image. Anatomical axes are indicated by the sagittal plane compass (right middle) and the guidelines linked to each set of slices. The inset at mid-left shows a cluster from case W.Y. triplicated with separate color mapping for greater clarity. B: 1 slice from each of the 4 blocks in A is shown with indicative thalamic nuclei obtained by superimposition of templates from the Morel atlas (reproduced by permission of John Wiley and Sons). See Fig. 2 for nuclear abbreviations.
The BIC. Figure 6

A modes to the ASPs and used Bayesian model comparison to observations, we fit functions with zero, one, two, three, or four modes. The outcome shows that there was no gross directional bias, in the DPC of either subject, for lower versus upper positions or leftward versus rightward positions ($t_{(14)} < 2.14, P > 0.05$).

The same analyses were performed for two additional, bilateral zones of thalamic activation, anatomically identified as mediodorsal (MD) and caudal intralaminar/parafascicular (Pf) nuclei (Supplementary Data/Discussion Section 2B and Fig. S8). Again, these pooled ASPs showed no evident spatial bias, across all hemispheres and all subjects. We could, however, discern a difference between the DPC, MD, and Pf in the proportion of voxels with multi-peaked ASPs: there were significantly fewer multi-peaked ASPs in Pf than in DPC and fewer still in MD (Fig. S6; Table S1). If a voxel’s ASP is broadly indicative of its population of spatially tuned neural
dimensional normality, we used Bayesian model comparison to determine the number of modes that best fit the data from a single voxel. The fits were obtained using gradient descent on the negative log posterior, yielding parameter values that maximize each model’s posterior probability. Appropriate checks were run for convergence and replicability. To the right of each plot is a bar representing the associated Bayesian information criterion (BIC), an approximation to the marginal likelihood that includes an Occam’s razor-like penalty for the number of parameters. The number of peaks yielding the smallest (least negative) BIC was selected as the best representation of each voxel’s response profile; here, the model with 2 modes (3rd from top). B: examples of selected models for other voxels with 0, 1, 2, 3, and 4 modes. Inverted Vs on the baseline of each outline box mark the peak position of each modeled mode.

Overall cluster in a complex fashion, such that an underlying map of polar angle is not readily deciphered. The bottom of Fig. 4A compares the pattern of positional specificities for a bilateral focus of activation extending dorsoventrally through central thalamus (involving mediodorsal and caudal intralaminar/nar nuclei). Both hemispheres show activation corresponding to all six test positions examined. However, again, the implied polar topography is either illegible (W.Y., right), and/or poorly consistent between the two sets of test positions (W.Y., left).

**Modeling voxel-based positional selectivity**

It was clear that many voxels appeared to be activated (at $P < 0.05$ FWE) by attentional shifts to more than one test position (e.g., Fig. 4A shows several instances of black voxels, indicating overlapping fields of activation from 3 test positions separated by 120°). Because we detected very little in the way of hemifield or quadrantary main effects, the inference was that individual voxels should have a multiple punctate responsivity of hemifield or quadrantic main effects, the inference was that each number of modes together with the BIC, which favors the two-mode model in this example. Figure 6B gives one example of a voxel best fit by each number of modes. If the zero mode (flat line) model is selected, it indicates that any modulation in the ASP is attributable to random error (noise); most likely the voxel is inactive to any attentional shifts (although a small minority might be active in a pandirectional manner).

Using the DPC cluster as an example, Fig. 7A shows the relative frequency of voxels best characterized by each number of modes. Consistent with the statistical parametric maps in Fig. 4A, the DPC clusters from the left hemispheres of subjects H.E. and W.Y. show many voxels with multiply peaked ASPs. In each case, voxels that are best fit by models with two or more modes outnumber those with a single or zero mode. For control data, we sampled the homologous region in the right dorsolateral thalamus of these two subjects (same dimensions but mirrored across the midline); these samples were mainly (~95%) composed of zero-mode voxels.

The ASP model fitting also provides a suitable tool for closer inspection and comparison of spatial bias in the attentional response of foci localized to particular thalamic nuclei. For instance, the polar plots of Fig. 7B indicate the relative overall response to each test position, compiled by pooling the ASPs of all voxels within the DPC cluster. Each ASP peak (whether taken from single, dual, triple, or quadruple peak profiles) contributes equally to the plot, which therefore records the relative frequency of peak responses to each of the 16 test positions. The outcome shows that there was no gross directional bias, in the DPC of either subject, for lower versus upper positions or leftward versus rightward positions ($t_{(14)} < 2.14, P > 0.05$).

**Fig. 5.** Attentional selectivity profiles of individual voxels. Three examples are shown, the plot of parameter estimate (PSC, parameter signal change) against cue position showing either a monophasic spatial modulation of response (left) or higher modes (middle and right).

**Fig. 6.** Model fitting of voxel attentional selectivity profiles. A: the result of fitting models with 0, 1, 2, 3, or 4 modes (top to bottom) to the data from a single voxel. The fits were obtained using gradient descent on the negative log posterior, yielding parameter values that maximize each model’s posterior probability. Appropriate checks were run for convergence and replicability. To the right of each fit is a bar representing the associated Bayesian information criterion (BIC), an approximation to the marginal likelihood that includes an Occam’s razor-like penalty for the number of parameters. The number of peaks yielding the smallest (least negative) BIC was selected as the best representation of each voxel’s response profile; here, the model with 2 modes (3rd from top). B: examples of selected models for other voxels with 0, 1, 2, 3, and 4 modes. Inverted Vs on the baseline of each outline box mark the peak position of each modeled mode.
clusters (around 20 voxels in size) were also accepted as valid. A small number of larger, single-position related activation, regardless of cluster size. Most clusters fell same, or separate, voxels) were accepted as genuine task set of six independent, single-position contrasts (Friston et al. 2005). Hence all foci with multiple position sensitivity (in the co-incidence of spurious activation at two or more test posi-

tions is a remote likelihood—just as expected for what is, in effect, a conjunction analysis for two or more effects within a set of six independent, single-position contrasts (Friston et al. 2005). Hence all foci with multiple position sensitivity (in the same, or separate, voxels) were accepted as genuine task related activation, regardless of cluster size. Most clusters fell into this category; a small number of larger, single-position clusters (around 20 voxels in size) were also accepted as valid.

The major limitations inherent in atlas-based nuclear profiling stem from individual anatomical variation. To gauge the level of accuracy obtainable, we used templates from two separate brains shown in the Morel atlas of human thalamus (Morel et al. 1997), deforming each to fit functional images from the subject (W.Y.) with the most activation in the equivalent plane of section (Fig. 3). The outcome showed very little inconsistency in the nuclei scored for activation by each template (for further examples and analysis, see Supplementary Data/Discussion Section 3A). Assuming that the deformed templates match our subjects as well as they match each other, compilation of the results across subjects should yield a reliable rank ordering of the likelihood of the activation of each nucleus under our task conditions.

Table 1 lists all nuclei with a frequency of activation across hemispheres and subjects of 75% or greater (i.e., a numeric score in the range 4.5–6.0; see Table 1 for a note on the scoring system.) This is sufficient to identify four major centers of activity that were commonly active bilaterally in all three subjects. These are 1) the parvocellular and paralamellar divisions of the mediodorsal nucleus (MDpc and MDpl) and adjacent parts of the central lateral (CL) and ventral lateral posterior (VLp) nuclei (also known, collectively, as the oculomotor thalamus); 2) the caudal intralaminar nuclei: parafascicular (Pf), subparafascicular (sPf) and center median (CM); 3) the medial pulvinar nucleus (PuM, including the DPC, plus additional foci); and 4) the posterior complex: medial geniculate, supragenicular, and posterior nuclei (MGN, Sg and Po). The full tabulation of these results, listing progressively less reliably activated nuclei, is given in Table S3.

To essay a semiquantitative measure of relative activation, we also charted the fraction of levels at which each nucleus was scored for activation, in each of the horizontal and sagittal series of the atlas. We report the product of these fractions, adjusted to estimate the fractional volume of activation (FVA) for each nucleus (see Supplementary Data/Discussion, Section Table 1. Subjective scores for the activation of specific thalamic nuclei (truncated at score < 4.5)

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<th>Nucleus</th>
<th>TOT</th>
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Analyzing a single anatomical plane, a score of 0.5 is awarded to a nucleus if there is at least one level at which it coincides with a focus (or foci) of activity, elicited by at least one test position. The analysis is independently replicated across two planes of section, in each of six hemispheres, to yield a maximum score of 6. Subsequent columns (CG, WY, and HE) report the sub-scores for each subject, pooled across hemispheres, and the sub-scores for each hemisphere (L, R) pooled across subjects. CL, central lateral; MDpc, mediodorsal (parvocellular division); PuM, medial pulvinar; Sg, supragenicular; MDpl, mediodorsal (paralamellar division); Pf, parafascicular; MGN, medial geniculate; VLp, ventral lateral posterior; CM, centre median; Po, posterior; sPf, subparafascicular.
DISCUSSION

Our aims were to map thalamic systems engaged in top-down control of covert spatial attention and to characterize their spatial resolution, distribution, and topography, using a partial report paradigm to distinguish between externally driven (visual) and internally instructed (attentional) neural activity. Extensive sampling of three subjects showed that a variety of thalamic sites respond to covert attentional shifts, whereas no such response was measured for visual stimulus induced effects. The profile of nuclear activation, identified by reference to the Morel atlas of human thalamus, closely resembles the pattern of thalamic connectivity of the cortical eye fields [particularly the frontal eye field (FEF)] in nonhuman primates (Huerta et al. 1986; Stanton et al. 1988; Tian and Lynch 1997). Tellingly, seven of the eight top-ranked nuclei listed in Table 1 constitute virtually the entire set of thalamic connections of the FEF—apart from one nucleus (the ventral anterior) that appears in the middle of Table S3. Full details and references for this anatomical parallel are provided in the Supplementary Discussion (Section 3E). The finding is reminiscent of previous accounts of substantial overlap between the cortical areas responsible for covert and overt shifts of attention (Corbetta 1998; Corbetta et al. 1998; de Haan et al. 2008); a fact that, added to psychophysical demonstrations of the general context of a visuomotor origin, how far can we rationalize the pattern and properties of thalamic activity evoked by covert attention?

Dorsal pulvinar

The sites of activation centered on dorsal pulvinar and mediodorsal nucleus (MD) are regions that are likely to be homologous to the principle thalamic zones reciprocally connected to the parietal and frontal eye fields, respectively, in nonhuman primates (see Supplement Section 3E). For the pulvinar, there is direct neurophysiological evidence of involvement in attentional mechanisms. A region known as dorsomedial pulvinar (Pdm) has neurons showing spatially specific, attentional modulation of responses to singly presented target stimuli (Petersen et al. 1985). Neurons in the same region were reported to “simply shut down” when the animal performed an attentive task (dimming detection) at fixation—i.e., in behavioral circumstances where spatial shifts of attention were suppressed (Bender and Youakim 2001). Electrode recordings from Pdm show that the receptive fields of sequentially encountered neurons can jump in irregular directions, sometimes by 20° or more (Petersen et al. 1985). If nearby neurons were to encode similarly distant attentional shifts, the collective sample of neurons within a single voxel could plausibly show a multiply peaked tuning function, as evident for ASPs obtained from the DPC. The fact that this particular site of activation (i.e., DPC) was unilateral (left hemisphere) is not attributable to differential sensitivity because, even at lower thresholds (uncorrected \( P < 0.001 \)), there was no activity at the corresponding site in the right hemisphere—or, in one subject, in either hemisphere. With a sample size of three subjects, it is hard to place any such inconsistencies in the context of the general population. The fact that the DPC showed significant effects for positions in all four quadrants of visual space is not incommensurate with previous studies showing left hemisphere activation by covert attention cued to single right or left hemifield locations (Hopfinger et al. 2000; Ikkai and Curtis 2008; Kelley et al. 2008; Perry and Zeki 2000). Despite the higher spatial resolution afforded by our stimulus design, with 16 test positions, we were unable to infer a specific polar angle map from the unmistakable signs of an underlying polar topography (e.g., as shown in the inset in Fig. 4). One corollary of these complex tuning functions in DPC, at both the voxel and nuclear levels, is that the pulvinar could have multiplexed maps in retinal and object based coordinates—a notion encouraged by the finding that dorsal pulvinar damage can simultaneously affect localization of targets in either frame of reference (Ward and Arend 2007).

Mediodorsal nucleus

The region of activation centered on MD could equally be ascribed to a zone of central thalamus termed the oculomotor thalamus (OccTh), because of its possessing neurons with a variety of spatially tuned presaccadic and postsaccadic discharge (Schlag and Schlag-Rey 1986; Tanibuchi and Goldman-Rakic 2005; Wyder et al. 2003). OccTh includes regions in and

3D). Pooling across subjects and hemispheres, the mean FVA for activated nuclei is shown in Fig. 8 (with a cut-off at 5%), along with the intersubject standard error. Of course, as in any imaging data, the volume of active voxels is contingent on the level of thresholding, so it is the rank ordering of the various nuclei, rather than the absolute values reported, that is of primary consideration. By the FVA measure, the parafascicular and paralamellar segment of the mediodorsal emerge as the most fully activated nuclei; overall, the outcome is in good accordance with Table 1, six nuclei being common to the eight most active by either means of evaluation.
around the internal medullary lamina, i.e., intralaminar nuclei such as the central lateral nucleus, and paralaminar parts of MD, VL (ventral lateral), and VA (ventral anterior) nuclei. There is a particularly notable comparison to be made between our results and data obtained from two studies (Watanabe and Funahashi 2004; Wyder et al. 2003) recording activity in MD or OcTh of nonhuman primates while performing a delayed saccade task (a paradigm in which subjects briefly withhold a saccade from fixation to a flashed target location). In a visuo-motor account of covert attention, the delay period (i.e., the interval between target flash and the release of the saccade) is one in which covert attention is effectively located on the saccade target (Awh and Jonides 2001). Also, the geometric design of the paradigm is similar, with a ring of target locations surrounding fixation (16 in our case and 8 in each of the 2 animal studies). A substantial proportion of neurons in both studies showed sustained, directionally tuned responses during the delay period, which might be regarded as functionally analogous to the activity recorded in our covert attention task. Fitting neural responses with Gaussian tuning curves, both studies concur that the full width half maximum measure of mean directional tuning was comfortably in excess of a quadrant; this contrasts with our finding that there is typically a narrow target location (i.e., a 22.5° sector) to which individual voxels activate most reliably; possibly, this optimal BOLD signal reflects a peak response in the composite local field activity investing comparably tuned human neurons. Finally, in agreement with the ASPs we plotted for single voxels, the distribution of neuronal preferred directions in monkey OcTh was fairly uniform. A slightly greater proportion preferred a contralateral direction, but there was no significant difference between hemifields (Watanabe and Funahashi 2004). As a footnote, the target eccentricity used in our study was smaller [i.e., 3°, compared with 6–20° (Wyder et al. 2003) or 17° (Watanabe and Funahashi 2004)], which is a potentially significant factor if neuronal response varies with target eccentricity, as well as polar angle, as reported by Wyder et al. (2003).

Parafascicular nucleus

Activation of the third region of thalamus, the caudal intralaminar nuclei centered on Pf, implies that our task also recruits thalamo-striatal circuitry, because these nuclei are known to be the principal thalamic source of input to the striatum (Fenelon et al. 1991; Gimenez-Amaya et al. 1995; Sadikot et al. 1990, 1992). The basal ganglia are known to be involved in attentive processes as indexed by various anomalies in cued detection tasks shown by subjects with degenerative conditions (Couette et al. 2008; Fielding et al. 2006; Filoteo et al. 1997; Yamaguchi and Kobayashi 1998). Parkinsonian subjects, for example, typically show hyper-reflexivity to exogenous cues (Briand et al. 2001; Fielding et al. 2006; Poliaffkoff et al. 2003), and this general oversensitivity to salient stimuli can be interpreted as a disorder of top-down control (Cools et al. 2010). Pf in particular has an excitatory influence on regions in the head and body of the caudate nucleus that also receive convergent input from cortical eye fields (FEF and SEF) supplementary eye field (Fenelon et al. 1991; Parthasarathy et al. 1992; Sadikot et al. 1992; Shook et al. 1991; Stanton et al. 1988). Hence the Pf may modulate the operation of the oculomotor loop, a closed circuit operating through cortex, basal ganglia, and thalamus (specifically FEF/SEF–caudate–ventrolateral SNr–VA/MDpl–cortex) (Alexander et al. 1986). Notably Pf is one of the two thalamic sites (the other being dorsal pulvinar) where pharmacological manipulation of GABA receptors is known to influence the speed of spatial shifts of attention, as shown by systematic effects on target detection latency under conditions of invalid spatial cuing in the Posner task (Minamimoto and Kimura 2002; Petersen et al. 1987). Sources of input to Pf, in addition to the cortical FEF, include brain stem structures such as the deep layers of the SC (Harting et al. 1980), the pedunculopontine nucleus (Lavoie and Parent 1994), and monoaminergic modulatory systems (Lavoie and Parent 1991; Rico and Cavada 1998; Vogt et al. 2008). The physiology of Pf is not well documented, but one study in alert macaques suggests a kind of alerting function, because relatively short latency (<90 ms) neural responses were found to unanticipated visual, tactile, and/or auditory stimuli—responses that rapidly habituated if the stimulus was repeated and bore no association with reward (Matsumoto et al. 2001). Thus Pf could be responsible for relaying the occurrence (rather than the nature) of an attention-worthy event into basal ganglia circuits (Smith et al. 2009b).

Posterior group nuclei

Activation of the fourth zone, centered on the posterior group of nuclei, includes structures affiliated with multimodal cortical fields and sensory inputs (Burton and Jones 1976) that have rather poorer credentials for mediating covert shifts of attention; indeed, their functional roles are not well established. Perhaps activity here could be linked to the integration of gravitometric cues in a multimodal representation of spatial alignment. The task subjects were required to perform might seem a hermetically retinal one, yet gravitational influence has been measured in a variety of visual tasks, including orientation pop-out, the Thatcher (inverted face) illusion, mental imagery, and estimation of vertical alignment (Lobmaier and Mast 2007; Lopez et al. 2008; Marendaz et al. 1993; Mast et al. 2003)—typically by altering the body position of observers, including the supine position used in the scanner. Thus the key to posterior group activity may lie in a differential engagement of mechanoreceptive input via the spinothalamic tract (Davison et al. 2008; Ralston and Ralston 1992) and/or vestibular input, specifically the magnocellular MGN (Hawrylyshyn et al. 1978), in reaction to varying cue locations.

Nonactivation of visual thalamus

Paradoxically perhaps for a visual study, we found very little evidence for activation of the two nuclei (LGN and inferior pulvinar) that have a demonstrably topographic representation of the visual field (Chen et al. 1999; Cotton and Smith 2007; Schneider et al. 2004), either in respect of visual stimulus driven activity or visual attentional modulation. Concerning the former, we know that the disc stimuli used in this study were capable of activating retinotopically appropriate voxels in cortical area V1/V2 (Hulme et al. 2009). However, compared with the reversing checkerboard stimuli typically used by studies that do successfully activate the LGN (Chen et al. 1999; Hess et al. 2009; Schneider et al. 2004), the discs were briefly

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presented (200 ms), offered weaker visual transients (because of their sinusoidal contrast modulation), and occupied a far smaller fraction of the visual field. Visual stimulation can generate BOLD signal changes that are ≥50% larger in cortex than in the LGN (O’Connor et al. 2002). Hence there is little anomaly in the ability of our disc stimuli to produce detectable activation in V1 but not LGN. The cue stimulus (a thin black line 1 deg in length) was still more tenuous. It also failed to produce a visual response, as indicated by the complete absence of significant activation in contrasts for main effect of cue direction applied to the control trials (where subjects viewed the same stimuli without performing the task).

The inferior pulvinar, rather like the LGN, is more robustly activated by stimuli with stronger visual drive, e.g., optic flow dot motion versus a luminance-disc transient (Cotton and Smith 2007). As with the LGN, the lack of a detectable visual response to our disc stimuli is not much of a surprise. Also similar to the LGN, it shows about 20% signal enhancement with attention (O’Connor et al. 2002; Smith et al. 2009a). Somewhat unfortunately, the inferior pulvinar falls just outside the range of the horizontal and sagittal series depicted in the Morel atlas; however, we infer that it was active, in the main effect of cue direction, in one case (CG-left; see Figs. S1 and S2, and Supplement for further discussion). The relevant cluster of voxels bore no features to distinguish it from any other site of activation, but it is, by virtue of its presumed visual input (and the failure of the LGN to activate), the only thalamic site where an attentionally modulated visual response could form a plausible component of the observed activation.

Re-entrant visual pathways

The re-entrant visual pathway passing from the superior colliculus (SC), via inferior pulvinar, to the ventral cortical areas liable to be forming disc percepts is a possible candidate for mediating covert attentional effects directed from frontoparietal cortex (Shipp 2004). The SC fell within our perithalamic region of interest, and its activation was also inconsistent, being marked in one subject alone (H.E.). The SC is known to be prone to pulsatile temporal signal artifact, and detection of its activation is further impeded by a local hemodynamic response function of apparent shorter time course (Wall et al. 2009). A more compelling reason why spatially specific activation of the subcortical re-entrant pathway reflecting target detection was not consistently observed is that it would depend on a conjunction of cue position (i.e., direction of attention) and target presence (Cotton and Smith 2007; Smith et al. 2009a). We documented the main effect of cue position, including 50% target-absent trials, likely diminishing the net activation of any re-entrant circuits engaged in target detection.

Conclusion

The collection of a high volume of fMRI data in a small number of subjects gave us the opportunity to perform a systematic, high-resolution, atlas-based audit of thalamic nuclei supporting covert visual attention. We found that the dorsal pulvinar, the paralaeamellar or oculomotor thalamus, and the parafascicular/caudal intralaminar nuclei each show robust and spatially specific attentional activation that seems particularly significant given their connectivity with the fronto-parietal eye fields of the cortex. The findings thus extend the anatomical basis for a visuomotor interpretation of covert attentional shifts (Awh et al. 2006; Moore et al. 2003) while also acting to broaden the prevailing corticocentric interpretation of attentional mechanisms.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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