Contralateral visual hemifield representations in the human pulvinar nucleus

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ABSTRACT

The pulvinar is a major nucleus of the thalamus. Macaque pulvinar includes two sub-regions that are connected to the visual cortex and are retinotopically organised, but the organising principles of the visual portions of the human pulvinar are unknown. We employed two tasks to address the question of whether human pulvinar exhibits spatial organization, using event-related fMRI. The first was a global-motion discrimination with a rich visual stimulus and the second a luminance-discrimination task of similar difficulty that used a minimal visual stimulus. Both tasks required central fixation and covert peripheral attention. A group analysis of BOLD responses elicited in the motion-discrimination task revealed activity bilaterally in the ventral pulvinar (z = 2 in Talairach space). Clear position-specificity was observed, with activity elicited only by contralateral stimuli. Ipsilateral stimuli caused suppression. This locus of activity is distinct from the more dorsal (z = 10) region of the pulvinar that has previously been reported to be visually responsive but not retinotopic. In the luminance-discrimination task, similar activity was seen but it was weaker and detectable only in the left pulvinar. In additional experiments with no task, passively viewed global-motion stimuli also activated the ventral pulvinar bilaterally. Our results show for the first time a distinct, bilateral visual representation in human inferior pulvinar that appears to be contralaterally organised.
INTRODUCTION

The pulvinar nucleus of the thalamus is connected with most of the cerebral cortex and is therefore assumed to perform integrative functions (e.g. Sherman and Guillery, 1996). Macaque pulvinar includes two sub-regions that are connected to the visual cortex and are retinotopically organised, together with at least one other visual region that is not retinotopic. Proposed functions of the visual pulvinar are to orient visual attention and to disambiguate relationships between stimuli within the visual field. In macaques, visually responsive neurons are found that have bilateral receptive fields (Petersen, 1985), suggesting that the proposed integrative function acts across hemifields. In humans, such a view is supported by fMRI studies showing increased pulvinar activity during tasks that distribute attention between hemifields, relative to those that do not (Kastner et al, 2004). Switching attention between bilaterally demanding stimuli results in task-related activity in left pulvinar and it is the parietal cortex that is thought to control these shifts (Yantis et al, 2002). The posterior parietal cortex makes reciprocal connections with the pulvinar in non-human primates (Asanuma et al., 1985; Baleydier and Morel, 1992), specifically, at the border of the nucleus termed PdM (pulvinar dorso-medial; Petersen et al, 1985). Units of this region exhibit bilateral receptive fields, fire during saccades to attended locations and have little (Petersen et al, 1985) or no (Bender, 1981) retinotopic organisation. The organisation of those portions of the human pulvinar that are active in attention-related studies share these characteristics, being reportedly without bias for spatial location of visual stimuli (Yantis et al, 2002; Kastner et al 2004). This suggests that the pulvinar region activated in these human studies may be connected primarily to posterior parietal cortex and may be homologous to macaque PdM.
More inferior (ventral), retinotopic portions of the macaque posterior pulvinar connect with occipital cortex. Here, the emphasis is on visual activity rather than attentional orienting. In contrast to more dorsal regions, a strong spatial organization has been reported. In each macaque pulvinar (left and right), two complete maps of the contralateral hemifield are found (Bender, 1981; Shipp, 2003). In humans, retinotopic maps have been found in multiple cortical areas (e.g. Sereno et al., 1995; Engel et al., 1997; Wade et al., 2002; Silver et al., 2005) and recently in the lateral geniculate nucleus (LGN; Kastner et al., 2004), but they have not been reported in the pulvinar. Our objective here is to examine the human pulvinar for retinotopic organisation. In macaque, neurons in inferior pulvinar can be driven by passive visual stimulation, but they are also strongly attentionally modulated (Petersen et al., 1985). For this reason, we combined a rich, moving stimulus designed to give strong visual drive with the use of a task performed at the same spatial location. We report the existence of a bilateral region in the inferior pulvinar that responds preferentially to contralateral visual stimulation. This result, taken together with primate results, suggests the presence of a retinotopic map.

**MATERIALS AND METHODS**

*Participants*

A total of 22 participants took part. Of these, all but one (age 38) were between the ages of 19 and 30 and all were in good health. They were screened according to standard procedures and informed consent was obtained. In Experiment 1, fourteen
participants (3 male, 11 female) were scanned. In Experiment 2, fourteen participants (6 male, 8 female) were scanned, of whom 6 also participated in Experiment 1. Experiment 3 was conducted in the same scan session as Experiment 1 and so the same fourteen participants were used.

**Visual Stimulation and Tasks**

Computer-generated visual stimuli were presented via an LCD projector on a screen at the end of the scanner bore and were viewed via a mirror mounted on the headcoil.

**Experiment 1: Motion discrimination**

In order to claim evidence for a retinotopic organization it is necessary, as a minimum, to show strong contralateral biases in symmetrical locations in the two pulvinar nuclei. The purpose of Experiment 1 was to seek evidence for such a pair of pulvinar sub-regions. Bilateral, retinotopically organised visual activity has not previously been reported in studies of human pulvinar. We used a large stimulus that contains motion as well as spatial structure and is expected to produce strong activation in multiple areas of visual cortex. Reasoning that feedforward and feedback connections to the cortex extend the length of the pulvinar, this rich stimulus should promote visual drive in the nucleus by virtue of its connections. Because of the pulvinar’s strong association with attention, we presented these stimuli in the context of a demanding task.
An event-related fMRI design with a variable inter-stimulus interval was employed. Participants maintained fixation at a central point present throughout data collection whilst performing a task involving detecting a change in the global motion strength of a random-dot pattern (5 deg diameter). Targets were presented for 3000ms and were centred at an eccentricity of 12.5 degrees to either the right or left of fixation. Each consisted of 200 white dots on a dark background. Each dot was 40 arc min in size and moved in a straight path for 133ms before disappearing and reappearing at a new, random location. 10% of dots were repositioned on each frame update. Local motion directions were controlled so as to create a global perception of optic flow. The stimulus was based on that of Morrone et al. (2000), in which optic flow varies over time, smoothly changing between expansion/contraction and rotation, via intermediate spiral motions. This stimulus activates both low-level motion sensors in areas such as V1 and V2 and also higher-level neurons sensitive to global flow structure, such as those found in primate MST (Saito et al., 1986; Duffy and Wurtz, 1991). The strength of the motion percept was manipulated by assigning random directions to a proportion of the dots (noise dots). During the first 1500ms of each trial, the signal strength was 50%. Mid-way through each presentation (i.e. after 1500ms), the proportion of noise dots was either increased to 70% or decreased to 30%, causing the perception of global motion to either strengthen or weaken. Participants had to maintain fixation throughout, and report whether motion strength increased or decreased by pressing one of two keys of a response pad immediately after the end of the trial. The two directions of change were equally probable and the direction was selected pseudo-randomly on each trial. Stimulus location (left or right) was also determined pseudo-randomly with equal probability. The location and time of onset of the trials were not pre-cued. The inter-trial interval varied (6s average)
according to the “long exponential” distribution of Hagberg et al. (2001). The average inter-trial interval was balanced for both target location (right/left) and motion strength change (increase/decrease). A single run lasted 8 minutes 19 seconds and consisted of 56 trials. Four runs per session were completed. Participants were instructed to maintain fixation at a simple dot throughout. Fixation itself was not meant to be attentionally demanding, and we purposefully did not introduce a task at fixation in any of our experiments to avoid the confounds this may introduce elsewhere in the visual field (Schwartz et al, 2005).

Prior to the experiment, each participant viewed a practice sequence outside the scanner. The responses were used to adjust the proportion of noise dots, where necessary, such that approximately 70% of responses were correct. For eleven participants, the standard proportions described above were used, while the remaining three participants required adjustments of 5%. Participants also had a short trial run in the scanner to confirm their ability to perform covert detection at the designated level.

Experiment 2: Luminance discrimination

Experiment 1 involved both strong visual drive and a demanding task. In Experiment 2, a demanding task was employed at each of two well-separated locations (left and right) in a similar fashion to Experiment 1, but a minimal visual stimulus was used.

An event-related fMRI design, similar to that of Experiment 1, was employed. Targets were presented for 1000ms at an eccentricity of 10 deg to either the right or left of the
fixation point, centred on the horizontal meridian. The target was a small (1.5 deg) circle of uniform luminance presented on a uniform background. The circle was brighter than the background and was easily visible. Mid-way through each presentation, the target luminance either increased or decreased by 12%. The participants’ task was to detect the direction of the change, whilst maintaining central fixation, and make a forced-choice response using a keypad. The magnitude of the luminance change was chosen to give a performance level of about 70%. On half the trials, determined randomly, luminance increased and on half it decreased. Similarly, half were presented on the left and half on the right. The location and time of onset of the trials were again un-cued. Between trials, the display was uniform apart from the fixation spot. The inter-trial interval varied in the same way as in Experiment 1. A single run consisted of 72 events, lasting 8 minutes 28 seconds and participants completed up to 6 such runs per session.

Experiment 3: Passive visual stimulation

In this experiment, motion stimuli similar to Experiment 1 were used to give strong visual drive but the task was removed. The objective was to test whether sustained passive visual stimulation is sufficient to generate pulvinar activity and, if so, whether it is contralaterally organised.

In order to enable us to determine whether visual activity is sustained in nature, or transient and related to stimulus onset, long stimulus presentations were used, in a block design. Activity was then modelled in two ways. Firstly, a conventional block-design analysis was performed to detect sustained activity and secondly the data were
re-analysed with a regressor modelling only transient activity at the onset of the block. The optic flow stimulus of Experiment 1 was used. The signal component was 70%, the same as the strongest flow component used in Experiment 1. Each stimulus was presented continuously for 15 seconds. Blocks of three types were used: motion in the right hemifield, motion in the left hemifield and fixation blocks with no motion stimulus. The sizes and locations of the stimuli were the same as in Experiment 1. Blocks with motion on the right and left were alternated, separated by fixation blocks to provide an inter-stimulus baseline condition. One run contained 7 left and 7 right blocks together with 14 fixation blocks. A buffer of ten seconds was used at the beginning and end of each run giving a total duration of 7 minutes 20 seconds. Two runs of this passive stimulus were viewed after the event-related scans of Experiment 1.

**Data Acquisition**

BOLD activity was measured at 3 Tesla (Magnetom TRIO, Siemens, Erlangen, Germany) using an 8-channel array headcoil and a standard gradient-echo, echoplanar sequence (TR = 2000 ms, TE = 34 ms, flip angle 90 deg). Axial slices were positioned so as to cover the entire thalamus as well as portions of the cerebral cortex. Voxel size was 2.5mm (isotropic). A high-resolution 3D anatomical scan (MP-RAGE, 1mm resolution) was taken at the beginning of each session.

**Analysis**
The data were analysed using BrainVoyager QX. Functional data were aligned to high-resolution anatomical scans, motion-corrected and slice-time-corrected. The first three volumes of every run were discarded to ensure a steady state. A high-pass filter was used to remove periodicities greater than three times the mean separation between events.

Both group analyses and individual analyses were performed. These have differing merits. A group analysis with spatial normalisation permits increased sensitivity to signals that may be hard to detect in a single scan on a single participant and gives increased confidence that the results will generalise to the population. However, individual analyses avoid the spatial blurring that is inherent to group analyses. The axis of the anterior-posterior commissure was defined in every participant and both functional and anatomical volumes were aligned with this axis before being subsequently normalised into Talairach space (Talairach and Tournoux, 1998) within BrainVoyager. The data were re-sliced using 3mm voxels.

In the case of the group analyses, Talairach-transformed data were spatially smoothed using a 4-mm FWHM Gaussian kernel. Transformed data from all subjects were then entered into a multiple regression analysis (random-effects which tests for between-subject differences in response). For Experiments 1 and 2, responses to all same-hemifield presentations were averaged and (a) contrasted with the inter-stimulus baseline and (b) contrasted to their contralateral counterparts. In addition, the responses to all events were compared to baseline. Baseline was defined as the average activity during a period of 4 seconds immediately preceding each event, the definition also used to calculate event-related timecourses. The criterion for statistical
significance employed was $p<0.01$ corrected for multiple comparisons (FDR) in all analyses. Pulvinar voxels meeting this threshold were included in the event-related timecourse plots. In Experiment 3, blocks containing stimuli on the right and left were independently contrasted with baseline blocks and were also contrasted with each other. To examine results for individual participants, a separate GLM analysis was conducted on the data without spatial smoothing for each participant in each experiment. These analyses were performed in Talairach space, to allow meaningful interpretation of locations, and the contrasts made were the same as those used in the group analyses.

In all experiments, regions of activity were identified within the pulvinar as defined by the stereotaxic atlas of Morel et al. (1997). Activity in other parts of the brain was not examined. For each cluster of active voxels identified, an average time-course was calculated reflecting the mean of all voxels in the cluster. For ease of comparison with other studies, the Talairach co-ordinates of these clusters are quoted where appropriate.

**RESULTS**

**Experiment 1**

The results of Experiment 1 reveal two small regions of activity in the inferior pulvinar ($z=1$), one in each hemisphere, each of which is active only when the participant performs the task in the contralateral hemifield. The existence of these areas is revealed very clearly and reliably in the group analysis involving all 14
participants. Figure 1 shows slices from the standard brain used for normalization, with significantly active voxels overlaid in colour. The activation is derived from contrasting left events with right, which detects only differential activation between the two sides; any activity that is present in both sides is discounted. The figure reveals activity in a region of left pulvinar (shown in blue) that is active during events occurring in the right hemifield and another area in right pulvinar (orange) in which activity is correlated with events on the left.

Figure 1

Figure 1 also shows the associated mean timecourses for the left and right voxel clusters shown in the brain slices. These show activity separately for left events (blue) and right events (red); the difference between them provides the basis of the significant differential activation in the voxels identified. It is of interest that not only does the contralateral stimulation yield a positive BOLD response, but ipsilateral stimulation shows a deactivation that is of a similar form, though smaller. This indicates clearly that the inferior pulvinar is very strongly biased toward contralateral events. At least for our stimuli, which were presented at an eccentricity of 10 deg, there is no ipsilateral response. Moreover, our result is suggestive of a suppressive response to ipsilateral stimuli. This finding is reminiscent of the negative BOLD seen in ipsilateral visual cortex during presentation of a lateralised stimulus (Smith et al., 2004). It should be noted that the timecourses are derived from the same data as the region of interest itself and that some people argue that this can exaggerate effects by introducing sampling bias.
When responses to events in both right and left hemifields were pooled and contrasted with baseline activity, the group analysis showed no significant activity in the inferior pulvinar in either hemisphere. This presumably reflects the fact that only half the events contributed positively to such a contrast, while the other half contributed neutrally or even negatively. Significant activation was seen, in both pulvinar (more strongly in right than left), when contralateral events only were contrasted with baseline (not shown). But the clearest results were obtained with the contralateral vs ipsilateral contrast used for Figure 1.

Since ventrolateral pulvinar is adjacent to the lateral geniculate nucleus (LGN), it is important to avoid mistaking LGN activity for pulvinar activity. Complete reliance on Talairach co-ordinates is unsafe, particularly in a group analysis. We therefore checked for the existence of a separate peak of activity in the LGN. This was clearly seen in the expected location, based on anatomical expectations together with previously published co-ordinates for functional activation (Kastner et al, 2004). Figure 2(A) shows the distinct peaks of activity in the two regions. The LGN is centred some 9 millimetres from the pulvinar, being more lateral as well as more ventral, as expected.

Figure 2

Figure 3 shows sample data from individual participants. When dealing with a small region of activation, a group analysis is not necessarily the most sensitive approach. Because of small differences in anatomy between brains, the activity may appear in different locations even after spatial normalization. The activity will then be spatially
blurred and may not reach statistical significance in a given voxel. Morel (1997) observes that positional variations are greater in lateral/posterior nuclei than elsewhere in the thalamus. However, variations may be significantly less than in the cerebral cortex, where group analyses are typically applied. Thus, whether a group analysis is beneficial is an empirical question.

Figure 3

As in the group analysis, we find activity in inferior pulvinar to be most prominent in individuals when contrasting right and left events. Contralateral activity was seen on at least one side in 13 of 14 participants. Activity was seen bilaterally in 6 of the 14 brains examined. Activity in individuals was examined in the Talairach-transformed brain as well as in native space, so that co-ordinates could be compared across brains and with the results of the group analysis. Table 1 shows, for each participant, whether inferior pulvinar activity was present and at what Talairach co-ordinates. For one participant (SC), a small cluster was present in native space but could not be observed in the Talairach-transformed brain; the co-ordinates given are in Talairach space but based on the former activation.

We also checked for the presence of a separate LGN activation in all individuals. In most cases, this could be found. Figure 2(B) illustrates separate activations in a single coronal slice in one participant.

Table 1
These results show that the use of lateralised complex motion stimuli results in activation of the inferior pulvinar in both hemispheres. They also show total specificity for contralateral stimuli, providing the first evidence consistent with retinotopic organization in the human pulvinar.

In the random-effects group analysis, significant activity was also seen in a more anterior/dorsal location, in the left thalamus only (-10, -17, 14). Unlike the more ventral region discussed above, this dorsal region was active when all events were contrasted with baseline and not when right and left events were contrasted with each other. However, this location is probably too anterior to be in the pulvinar and is close to the ventro-posterior nucleus (VPL) of Morel (1997), which has been associated (based on its connectivity) with motor functions (Johansen-Berg et al., 2005). Given that our participants were responding via a button pad with the right hand and activity was seen only on the left, but for all events, this activity may be related to motor aspects of the task.

Although some previous studies (Kastner et al, 2004; Villeneuve et al, 2005) have reported activity in more superior portions of the pulvinar, only one study (Yantis et al, 2002) has previously reported visually related activity in the inferior pulvinar, and then only on the left. The inferior right pulvinar has not previously been activated by any paradigm to our knowledge. Other studies reporting right pulvinar activity do so only at more superior locations. In our random effects analysis we did not see activity in the region of superior pulvinar identified as active during attentional engagement by Kastner et al. (2004). Even with fixed-effects analysis, a less stringent analysis that does not test between-subject variability, only a small cluster was evident, seen when
all events were contrasted with baseline (i.e. not retinotopic). Presumably our paradigm is not optimal for activating this region. The relationship of our results to activity shown in previous studies will be considered in the Discussion.

**Experiment 2**

In Experiment 1, rich visual stimulation was combined with a demanding task, in order to maximise pulvinar activation. This leaves us not knowing whether the activity observed reflected passive visual stimulation, task-related factors, or both. Experiment 2 retained the task requirement of Experiment 1 but, in contrast to Experiment 1, it minimised visual drive by using a small, uniform, static target. If the results were similar to Experiment 1, it would suggest that strong visual drive is not essential for activating the contralaterally organized pulvinar regions we have defined in Experiment 1. In fact, the observed activation was much weaker.

As in Experiment 1, which also used an event-related design, a group analysis was performed using two different contrasts: all events vs. baseline, to detect event-related activity that is not spatially organized, and right events vs. left events, to detect activity that is spatially mapped. The right vs. left analysis revealed activity in the left posterior/ventral pulvinar, corresponding to the region identified in Experiment 1, but it was weaker than in Experiment 1 and absent altogether in the right pulvinar.

Figure 4(a) shows an axial slice at Talairach plane z=2. Superimposed are active voxels from a random-effects group analysis in which right and left events were
contrasted. In the left pulvinar, a small cluster is significantly active at the posterior/medial boundary of the pulvinar (-10, -31, 2). This region exhibits strong responses to contralateral (right) events but suppression for ipsilateral (left) events. This is shown in the associated timecourses in Figure 4(b). The peak is close to the region found to be active in Experiment 1 (-11, -28, 1) and it is therefore likely that they reflect the same functional unit. As in Experiment 1, a suppressive effect is seen during ipsilateral events (blue timecourse).

Figure 4

The absence of activity in the right pulvinar raises the question of whether activity is truly absent or is simply below threshold. Random-effects analysis has low sensitivity when sample size is modest and it is always possible to fail to detect activity. Figure 4(c) shows the same axial slice, this time with significant voxels from the equivalent fixed-effects analysis. There is still no activity in right pulvinar, either on this or nearby slices. However, the left focus evident in Figure 4(a) is considerably larger, extending in the anterior-lateral direction. It remains compact in the dorsal-ventral dimension however (not shown), having more the shape of a cylinder than a sphere. An interesting interpretation emerges from examination of the layout of the retinotopic maps found in primate pulvinar (Bender, 1981; Shipp, 2003). According to Shipp (2003), the caudo-medial to rostro-lateral axis forms an “axis of isorepresentation”. That is, as one moves along this axis, one moves through the connection zones of different visual areas, with no change of visual field location. This gives rise to the possibility that the extended focus seen in Figure 4(c) reflects activity in different connection zones.
The results for individual participants mostly show no activity. Activity was present in only one hemisphere at the level of $p<0.01$ corrected, and in one other at $p<0.02$. In Experiment 2, the added power of a group analysis was required in order to detect activity whereas in Experiment 1, significant activity was seen more often than not in individuals (see Table 1).

These results confirm the demonstration (Experiment 1) of the existence of a contralaterally organized region in inferior pulvinar, but do so only in one hemisphere. Activity (measured in terms of cluster size) in the inferior left pulvinar is substantially weaker during the luminance-discrimination task of Experiment 2 than the motion-discrimination task of Experiment 1. Since the task difficulty is similar for the two tasks, the greater activity in Experiment 1 may reflect greater visual drive from the motion stimulus, which was both larger and richer. However, such comparisons are difficult since (a) the pool of participants was not the same and (b) there are various factors affecting sensitivity that may vary from scan to scan. It should be noted that medial inferior pulvinar makes dense reciprocal connections with MT in macaques (Shipp, 2001), so it is possible that motion stimuli provide greater activation for this reason.

No reliable activity was seen in superior pulvinar in Experiment 2, even when using a fixed-effects analysis. As in Experiment 1, activity was seen in left thalamus in the region of VPL (-11, -20, 13), probably related to button-pressing with the right hand.
Experiment 3

In Experiment 3, motion stimuli were presented and viewed passively, with no task other than fixation. Stimuli were presented in a block design in order to examine whether visual sustained visual responses occur in the pulvinar in the absence of endogenous attention or other task demands. A group analysis was conducted in which each stimulus block (left or right) in turn was contrasted with baseline blocks. Right and left stimulus blocks were also contrasted with each other.

The results of a random-effects group analysis in which responses were modelled conventionally (a boxcar profile convolved with the haemodynamic response function) provide further, strong support for the existence of a map of contralateral visual space within both inferior pulvinar nuclei. Where left-stimulation blocks only are contrasted with baseline (fixation) blocks, right inferior pulvinar is active (coordinates 19, -25, 1), while the left pulvinar is not. Similarly, activity in left inferior pulvinar (-21, -25, 2) is evident when right events are contrasted with baseline, while right pulvinar activity is absent. The same bilateral activity emerges strongly when right and left-stimulation blocks are contrasted with each other. This is shown in Figure 5. As in Experiments 1 and 2, this contrast tests for contralateral specificity. In this case, the peak of the activity is at 16, -28, 2 (right) and -22, -27, 5 (left).

Figure 5

The results, in common with those of Experiment 1, suggest that motion stimuli are mapped contralaterally in the inferior pulvinar. Activity is seen despite the absence of
a task, although attention was unconstrained and participants may have attended the stimuli to some extent.

The associated timecourses (also shown in Figure 5) show sustained activity, consistent with sustained visual drive rather than a transient alerting response. However, this may be because the model used in the analysis assumed sustained activity and therefore picks out those voxels that show it. To cover the possibility that there is transient activity in some voxels, we repeated the analysis of Experiment 3 using a model that contained only an impulse (convolved with a haemodynamic response function) at the onset of each stimulus block. This resulted in significant LGN activity, but not pulvinar. The lack of transient pulvinar activity confirms that visual drive in the inferior pulvinar is sustained in nature, at least in response to time-varying optic flow.

In the right pulvinar, the timecourses show clear suppression of activity during ipsilateral stimulation (lower right panel, red trace), as seen in Experiments 1 and 2. This is not evident in left pulvinar, however in this case the timecourses are drawn from a very small cluster of voxels and so lack sensitivity.

In both left and right pulvinar, the location of the active region is similar to Experiment 1 (no right pulvinar activity was seen in Experiment 2) but slightly more lateral and anterior. It is close to the antero-lateral end of the area identified in the fixed-effects analysis of Experiment 2 and shown in Figure 4(c).

No activity was seen in superior pulvinar in Experiment 3.
Comparison of results across experiments

Our three experiments reveal activity in broadly the same regions. However, close comparison reveals a systematic variation. This is shown in Figure 6, which summarizes the results from all experiments. The various locations for activation are remarkably circumscribed in the z dimension (dorsal-ventral), all being within 1 or 2 mm of z = 2. But in both x and y dimensions, the location of activity is much more variable. Figure 6 represents an axial slice at z=2 showing this variability. When the locations of activity, as determined by random-effects analysis (solid colours) are compared, it is evident that they are aligned on an axis that runs posterio-medial to antero-lateral and that the alignment is symmetrical in the right and left pulvinar. Activity from Experiment 3 (passive visual stimulation) is the most antero-lateral, being located in the portion of the pulvinar that is adjacent to the LGN. Experiment 2, in which there is a demanding task but less visual stimulation, activates the most postero-medial location. Experiment 1, which involves both strong visual drive and a task, gives peak activation at an intermediate location. Interestingly, when the active regions contained in the less-stringent fixed-effects analysis are examined (coloured outlines), it is not the case that they are centred on the corresponding solid coloured regions. Rather, they tend to spread towards the antero-lateral end of the pulvinar. This is most obvious in the left pulvinar, where all three experiments produced activation, but results from the right pulvinar are consistent.
Careful work by Shipp (2001, 2003) in the macaque pulvinar has demonstrated an organizational structure running along this same axis. The extreme antero-lateral portion, adjacent to the LGN, is strongly connected with cortical area V1. As one proceeds in the postero-medial direction, the cortical connection zones move through an orderly sequence (V1, V2, V3, V4), albeit with substantial overlap. Visual field location is invariant in this dimension, being mapped in the two orthogonal dimensions. Thus, a line drawn in this axis joins points that represent the same field location but with connections to different cortical visual field maps. Shipp referred to this as an “axis of isorepresentation”. We propose that the same organization may exist in the human pulvinar. Hypothetical axes of isorepresentation are marked on Fig. 6. However, the evidence is limited and the hypothesis is tentative.

On this interpretation, the systematic sequence of random-effects activations across experiments suggests that passive viewing activates primarily pulvinar tissue that is connected to early visual areas, whereas when attention is emphasised, tissue connected with higher visual areas is most active. The fact that it spreads preferentially towards V1-recipient pulvinar in a less stringent analysis, rather than spreading equally in all directions as is often seen in the cortex, suggests that antero-lateral pulvinar is always active in visual tasks but the degree of spread towards portions that connect with higher visual areas depends on the level of attentional engagement.

DISCUSSION
Lateralised visual maps in the pulvinar

We have provided the first fMRI evidence of contralateral organization in the human pulvinar. At the posterior/ventral margin of the pulvinar, a small region of visual sensitivity exists bilaterally, with sensitivity only to stimuli in the contralateral visual hemifield. Ipsilateral stimuli do not drive this region and, indeed, appear to suppress it. We will refer here to this region as the contralateral zone of the pulvinar (CZP). Contralateral specificity may indicate the presence of a complete map of visual space, as found in posterior/ventral macaque pulvinar. But because of the small size of the CZP, confirmation of the presence of a full map of space may have to await technological improvements in fMRI measurement.

In view of the trend for greater activation in the left than right pulvinar (Table 1 and Experiment 2), it is important to question whether the contralaterally organized zone of the pulvinar is truly bilateral and symmetrical. In general, more fMRI studies show left- than right-pulvinar activity, whereas this is not true of PET studies. It is worth mentioning a possible MRI-specific methodological interpretation of this. If the location of the pulvinar varies between participants more on the right than on the left, or if the location of a particular zone within the pulvinar varies more on the right, group significance may be lost in the right pulvinar, given that the focus of activity is small. In the case of PET, spatial resolution is inferior and this artefact may be absent because the differences in variance of localization are not resolvable. However, in Experiment 1 the left cluster was more prominent than the right in most individuals (Table 1), suggesting that it is not an artefact of group analysis.
One possible explanation of the apparent left-bias in our data is that it does not reflect properties of the contralateral region itself, which is expected to be symmetrical, but instead reflects contamination from more dorsal pulvinar regions that are asymmetric. Consistent non-retinotopic activation of a pulvinar region centred some 7-8mm more dorsally indicates a separate superior region responsive to both left and right events, i.e. with bilateral fields (Kastner et al., 2004). This should not cause an artefactual asymmetry in the contralateral region due to spread of the BOLD response and/or localization errors relating to normalization, because it exists bilaterally. But a third, separate area with some specific role in spatial attention might exist on the left, and this might artificially boost measured activity in the left contralateral area. Despite symmetrical anatomical connections, the contribution of attention to pulvinar drive could result in laterality of function in pulvinar. Even if cortico-pulvinar connections are symmetrical, laterality of parietal function coupled with parietal interconnections with the pulvinar (Asanuma et al., 1985; Schmahmann and Pandya, 1990; Baleydier and Morel, 1992) may result in asymmetric pulvinar activity. Additionally, the pulvinar is a large nucleus and, taken together with existing data, our experiments suggest that there are multiple compartments of attentional and visual drive within the pulvinar.

Because of the historical association of the pulvinar with attention, and the existence of a more dorsal pulvinar sub-region with clear dependence on spatial attention (Kastner et al, 2004), we have examined the influence of task demands that include a likely requirement for covert spatial attention on the CZP, as well as documenting visual drive. Attentional facilitation is known to occur retinotopically in cortex (Tootell et al., 1998; Slotnick et al., 2003) and has recently been shown to be specific
to the size of the attended target (Bles et al, 2006), so specificity for location and size may be expected for attentional effects, as well as for visual drive. We tentatively suggest that, of the two influences, visual drive may be dominant in CZP, provided a suitable visual stimulus is employed. A rich, complex global-flow stimulus gives strong visual drive, whether it is attended (Experiment 1) or not (Experiment 3). But when visual drive is minimised, to isolate effects of attention (Experiment 2), activation is weaker and (at least for our particular luminance discrimination task) only detectable in the left pulvinar. It is even possible that task demands made little or no contribution to the CZP activity we report, despite an undeniable role elsewhere in posterior pulvinar. After all, our minimal stimulus did have a spatial form, an onset, an offset and a luminance transition in the middle of the presentation. However, this question is far from resolved. Further experiments will be required to probe the roles of attention and visual drive more directly, perhaps by pitting them against each other in the same experiment.

The sustained time-courses seen in response to 15-second “block” stimuli (Experiment 3; Figure 5) show that the CZP does not respond in a solely transient manner. If CZP activity does, to some extent, reflect spatial attention, then this activity largely reflects sustained attention, rather than a transient orienting signal. The electrophysiology of primate pulvinar also suggests sustained visual response time-courses (Petersen, 1985).

Relation to other studies
Several studies have previously documented visual responses in human pulvinar but none has previously succeeded in finding the zone of retinotopic organization that is expected, based on primate studies. Possibly this is due in part to some aspect of data acquisition, or to the use of insufficient numbers of participants. But more likely it is due largely to the stimulation protocol. Our success is probably attributable to the use of a stimulus that is richer, in both spatial and temporal domains, than has been used before in this context. When this stimulus was not used (Experiment 2), only weak, unilateral activity was seen. Kastner et al. (2004) presented flickering checkerboard stimuli to each hemifield in turn, with passive viewing, and reported no activation in the pulvinar. When they presented similar stimuli to both hemifields and alternated attention between the two sides, they found bilateral attention-related activity in a dorsal region of posterior pulvinar (average $z$ co-ordinate = 10). We found only weak signs of activity at this location. Two stimulus differences may explain the difference between the results of their study and ours. First, by exclusively stimulating the peripheral visual field, we expect to selectively activate units with well-separated receptive field locations. Kastner et al. used checkerboards spanning 1.5 to 12.5 degrees; in this case a between-hemifields contrast may preclude differential activation because units with receptive fields near the vertical meridian may be activated by both right and left stimuli. But the key reason for the different result may be simply that inferior pulvinar is inefficiently driven by flickering checkerboard stimuli, but strongly driven by optic flow stimuli, possibly reflecting its known strong connections with the MT complex.

The presence of CZP only in the left hemisphere in Experiment 2 is reminiscent of a previous report of activity lateralised to left pulvinar during attentional switching.
between right and left (Yantis et al., 2002). The concurrence of Talairach co-ordinates between the two experiments is notable. This is one of only two fMRI studies, to our knowledge, to have reported pulvinar activity as ventrally as z=2. Our stimuli were all unilateral, so it is difficult to compare our results directly with theirs. However, two factors make us wonder whether we and they are in fact documenting different functional regions, despite the similarity of co-ordinates. Given that location can vary to some extent across brains, this is not impossible. The first factor is that their time-courses for shift-to-left and shift-to-right are similar; this is their basis for asserting lack of spatial selectivity in the left pulvinar. This is far from the case in our CZP. Time-courses for left and right stimuli (Figures 1, 3, 4 and 5) are quite different, one being excitatory and the other inhibitory. The second is the fact that they report transient, rather than sustained activity. This latter property clearly does not pertain in the lateral portion of our CZP during Experiment 3, which, as previously noted, shows that activity is sustained (Figure 5). It may be significant that while the response time-course for right CZP is quite flat, that in left CZP could be interpreted as the sum of a sustained response, similar to that seen on the right, and an early transient component. If this is the case, it is possible that our Experiment 3 and the Yantis et al. study do indeed identify different functional regions but that our left CZP cluster contains some voxels belonging to that of Yantis et al. (2002). Against this, such voxels ought to be excluded by a left vs. right contrast if their timecourses are similar for both. Also, it is odd (on this interpretation) that there is no sign of positive-going transient activity for ipsilateral stimulation; this shows suppression from the onset of the stimulus. We therefore think that such an interpretation is unlikely.
One other fMRI study has reported activity in the posterior pulvinar. Fan et al. (2005) used a task designed to separate different aspects of attention. They found activity relating to executive control while performing a visual judgement in the left pulvinar, at a lateral location (-22, -27, 3) consistent with the more lateral portion of left CZP. The task is so different, that again it is hard to know whether this is truly the same functional zone. Several PET studies are also relevant to our work, although they do not allow reliable distinction between the ventral and dorsal zones we have discussed. Some have associated the pulvinar with attention and arousal (LaBerge and Buchsbaum, 1990; Sturm et al., 1999; Bundesen et al., 2002) but, interestingly, two have found strong responses to motion stimuli with a global structure (Beer et al., 2002; Villeneuve et al., 2005). The left-bias evident in some fMRI studies is not prominent in the PET literature; indeed some studies report greater activity in right pulvinar than left (Sturm et al., 1999; Barrett et al., 2001).

Finally, one neuropsychological study is relevant. Ward et al. (2002) documented the effects of circumscribed unilateral damage to the dorsal anterior boundary of the right pulvinar, which produced an attentional deficit restricted to the lower left visual field. This supports the presence of contralateral topography, and indeed suggests further subdivision of the map into quadrants and presumably a full map; however the lesion in this patient appears to be rather more anterior than CZP. An upper-lower quadrant differentiation is also, more loosely, supported by fMRI studies of the ‘filling in’ phenomenon, in which regions in both right and left pulvinar are active during discrimination in the upper hemifield to a greater extent than in the lower hemifield (Mendola et al, 2006). How the organisation of CPZ might represent upper and lower space is the subject of current work in our lab.
Conclusion

We have described a small, bilateral region of the human inferior pulvinar that responds exclusively to contralateral visual stimuli. We provisionally call it CZP (contralateral zone of pulvinar). It is distinct from previously reported attention-related regions of pulvinar activity and it is characterised by visual sensitivity, both in the presence and in the absence of attention. We also present tentative evidence for an organizational structure within CZP that shares commonalities with the retinotopic zone of macaque inferior pulvinar. That we have been able to demonstrate contralateral specificity in human pulvinar is most likely due to the use of stimuli that provide very strong visual drive. Our data support the existence, within the posterior human pulvinar, of functional compartmentalisation on a scale of a few millimetres.

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**Table 1**

Results from Experiment 1. The locations of inferior pulvinar cluster peaks are given in Talairach space for 13 participants. A null entry means that no significant cluster was found; the 14\textsuperscript{th} participant had no active cluster in either pulvinar. All clusters meet the minimum statistical criterion of $p < 0.01$ corrected (FDR). Also shown is the volume of each cluster. In each case, the first number is the number of voxels that
reach this statistical criterion and the second number is the corresponding volume in mm$^3$. 
FIGURE LEGENDS

Figure 1
Bilateral activity in the human inferior pulvinar. Results from the random-effects group analysis of Experiment 1 are shown, thresholded at $p < 0.01$ corrected for multiple comparisons (FDR). A complete axial slice ($z=1$) is shown, together with sections at higher magnification in both axial ($z = 1$) and coronal ($y = -28$) planes. Voxels in which greater activity is seen during left events than right events are shown as orange/yellow, those with the reverse preference are shown as blue/green. The convention is radiological (left hemisphere on the right). Voxels with a positive correlation for left events emerge in the right inferior pulvinar (8 voxels, centred at TAL 16, -28, 1) while voxels with positive correlation for right events emerge in the left pulvinar (12 voxels, centred at TAL –11, -28, 1). The associated average timecourses are also shown, separately for left and right hemispheres. In each case, timecourses for right-hemifield events are in red, left-hemifield events in blue. These show negative activity for ipsilateral events as well as positive responses to contralateral events. Error bars show ±1 SEM.

Figure 2
(A) Montage of axial (horizontal) slices in three different planes, showing that the pulvinar activity seen in Experiment 1 (group analysis) appears distinct from the LGN. The convention is again radiological (left pulvinar shown on the right). The upper pair of images show the pulvinar activity evident in Figure 1, using the same colour code. The bottom pair show LGN activity in the same experiment, at a more ventral location (TAL 21, -23, -3 on the right, and –20, -25, -5 on the left). The middle pair show an
intermediate slice with no activity, demonstrating that the pulvinar lateralisation is not merely an artefact arising from blurred LGN activity. (B) A similar demonstration in the brain of an individual participant (JR), shown in the coronal plane at $y = -27$. Separate pulvinar and LGN activities are clearly seen in the left thalamus (thresholded at $p<0.05$ FDR), centred at $-10$, $-28$, $3$, and $-20$, $-25$, $-3$ respectively.

**Figure 3**

Results from two individual participants (a and b) exhibiting both right and left inferior pulvinar activity in Experiment 1. Both are transformed into Talairach space. In both cases, right and left hemifield events are contrasted (colour key as for Fig. 1) and activity associated with contralateral stimuli is evident. As well as extensive activity in visual cortex, activity in ventral pulvinar is apparent (arrowed). In each case, the associated timecourses are shown. These show suppressive responses to ipsilateral stimuli as well as excitatory responses to contralateral stimuli.

**Figure 4**

Results from Experiment 2. (a) Results of a random-effects group analysis, shown in the axial plane at $z=2$. As well as occipital activity, a region of interest located in left caudo-medial inferior pulvinar is evident when responses to right events are contrasted against left events. Results are threshold at $p<0.01$ corrected (FDR). The colour key is the same as for Figs. 1-3. (b) The event-related timecourses for this caudo-medial pulvinar region show increased activity for contralateral events (red) but not ipsilateral events (blue), which cause suppression. (c) The same slice as in (a) but with active voxels based on a more liberal (fixed-effects) statistical analysis.
**Figure 5**
Results of a group analysis of Experiment 3. **Left:** axial slices showing active voxels in the inferior pulvinar when right-stimulation blocks are contrasted with left. Orange and yellow indicate left>right, blue and green indicate right>left. The top and middle panels show two slices from a random-effects analysis, chosen to show activity on the left and right respectively. The left pulvinar shows a small focus (blue, arrowed). The right pulvinar shows a somewhat larger one (yellow). The bottom panel shows the same data using a fixed-effects analysis. The left and right activations are both more extensive and both are visible on the same slice. All results are thresholded at p<0.01 corrected (FDR).
**Right:** The timecourses associated with the two arrowed clusters (left and right pulvinar) emerging from the random-effects analysis. Blue: left stimulus, red: right stimulus.

**Figure 6**
Summary of results of the three experiments. The images represent right and left portions of an axial slice through the posterior thalamus at a level of z = 2. In each case, the grid is a 1mm grid and the co-ordinates are Talairach co-ordinates. The regions showing activation specific to contralateral events are shown in colour for Experiments 1 (blue), 2 (green, left pulvinar only) and 3 (red). In each case, activity present in a random-effects analysis is shown as a solid coloured patch and that present in a (less stringent) fixed-effects analysis is shown as an outline of the same colour. The thick black line represents the posterior boundary of the thalamus. The black arrow represents a hypothetical axis of isorepresentation (see text).
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