

## Thalamocortical circuits: fMRI assessment of the pulvinar and medial dorsal nucleus in normal volunteers

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### Abstract

This fMRI study investigates the activation of the thalamic nuclei in a spatial focusing-of-attention task previously shown to activate the pulvinar with FDG-PET and assesses the connectivity of the thalamic nuclei with cortical areas. Normal right-handed subjects (eight men, eight women, average age = 32 years) viewed four types of stimuli positioned to the right or left of the central fixation point (left hemifield-large letter, left hemifield-small letter display with flanking letters; right hemifield-large letter, right hemifield-small letter display with flankers). BOLD responses to small letters surrounded by flankers were compared with responses to large isolated letters. To examine maximum functional regional connectivity, we modeled “subject” as a random effect and attained fixed effect parameter estimates and *t*-statistics for functional connectivity between each of the thalamic nuclei (pulvinar, medial dorsal, and anterior) as the seed region and each non-seed voxel. Greater BOLD activation for letters surrounded by flankers than for large letters was observed in the pulvinar as anticipated and was also marked in the medial dorsal nucleus (MDN), anterior and superior cingulate (BA24 and BA24'), dorsolateral prefrontal cortex, and frontal operculum and insula. For the MDN, maximal functional connectivity was with the dorsolateral prefrontal cortex; correlations with left superior temporal, parietal, posterior frontal, and occipital regions were also observed. For the pulvinar, maximal functional connectivity was with parietal BA39; for anterior thalamus, with anterior cingulate.

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The thalamus comprises multiple nuclei that relay and filter sensory and higher order inputs to and from the cerebral cortex and limbic structures [17]. Two of the nuclei visible on MRI – the mediodorsal nucleus (MDN) and the pulvinar (major association nuclei or regions) – are of particular interest because of their reciprocal connections with prefrontal and temporal regions. The MDN has prominent interconnections with the dorsolateral prefrontal cortex (PFC) [11]. Indeed, the connections of the MDN have been used to define the PFC [30], a key area of executive action and attentional focus (cf. [3]). Crosson [7] suggests the MDN as a critical element in an attentional “selective engagement” system that impacts semantic functions

in schizophrenia. The pulvinar also contributes to frontal innervation [12,29].

The pulvinar, important in visual and possibly auditory attention [13,28,34], has prominent interconnections with the parietal and temporal lobes. The posterior parietal lobe is involved in judgments of the location of objects in space (see review [21]). The anterior thalamus has links with both the cingulate and the PFC-regions that contribute to specific aspects of visuospatial attention and short-term spatial memory [32]. Thus, a system that detects targets in a specific location surrounded by distracters should involve these systems. The pulvinar's role in enhancement or modulation of attention to spatial location is known from primate research (cf. [27]), FDG-PET studies [21] and fMRI studies [18,23,37]. Our earlier FDG-PET report posited the pulvinar as the subcortical structure that interact with cortical structures when a visual identification task requires the

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separation or filtering of a target object from surrounding objects [21], a concept that has recently been further developed [20]. Selectivity was assessed in these studies by presenting letters surrounded by an array of flanking letters (termed “SMALL” below) and contrasted with one large isolated letter (a condition in which selectivity is not required, termed “BIG”). Our goal was to replicate earlier FDG-PET findings using an identical fMRI task that would permit examination of the functional connectivity of the pulvinar, anterior thalamus, and MDN using the multiple activity assessments within each person. While connectivity between key regions such as the pulvinar with the cortex can be calculated with FDG-PET data, these values must be analyzed *across subjects* because there is only one activation value per subject; with fMRI, there are a number of BOLD runs per subject, allowing *within-subject* regional connectivity to be computed. With across-subject FDG analysis, stable trait-like regional intercorrelations could result from factors largely or entirely independent of connectivity. Brain-activity differences related to cytoarchitecture, mechanical accidents of growth, or common neurochemical, cerebrovascular, or glial factors could produce similarities in activity or size between two brain regions that did not result from direct pathways. With fMRI, the availability of multiple runs allows functional connectivity to be assessed within each subject across behavioral conditions and for regional covariation with task to be assessed.

Thalamocortical connections have been hypothesized as potential sites of defective interaction in neuropsychiatric disorders, including schizophrenia. Extensive connections of the ventral anterior nucleus and the MDN with the PFC, as well as the possible role of the thalamus in regulating sensory input, make fronto-thalamic regions an interesting area for investigation [17]. Although auditory, visual and somatosensory pathways primarily pass through the ventral posterior and geniculate nuclei, the complex associational thalamo-cortico-thalamic loop of the lateral orbitofrontal and dorsolateral prefrontal cortices independently involves the MDN and the pulvinar. Investiga-

tors [1,4–6,31] have advanced the concept that schizophrenia may involve faulty processing or filtering of sensory signals from input to the cortex via the thalamus. The important role of the MDN and pulvinar in attention was demonstrated in our PET study of the pulvinar [21], recent fMRI studies by others [14,26] and our current fMRI data in normal subjects. Normal-versus-patient fMRI activity differences in the thalamus [2,15], as well as connectivity differences between thalamus and cortex assessed by fMRI [31] and PET [19,22,24], have been demonstrated. Taken together, these studies indicate that explorations of differences among regions within the thalamus and of their cortical connectivity in normal subjects may lead to refinements in our concepts of disease.

Sixteen normal right-handed participants (eight men, eight women, age = 23–50 years, average = 32.3, S.D. = 8.3) all had normal vision and left-to-right reading habits. Echoplanar images were acquired with a multi-slice 2D-EPI sequence (128 × 28 matrix, TR = 2 s, TE = 40 ms, flip angle = 90°, FOV = 23 cm, slice thickness = 5 mm, skip = 2.5 mm) yielding 14 slices. Anatomical MRI acquisition used GE-LX-Horizon 1.5T SPGR sequence (repetition time = 24 ms, TE = 5 ms, flip angle = 40°), for contiguous 1.2-mm-thick axial slices, with a 256 × 256 pixel matrix in a 23-cm field of view, and chosen for maximal field flatness and gray/white discrimination.

There were four experimental runs on the same day, each 264 s in duration. Subjects looked at stimuli positioned horizontally at 2° to the right or left of the central fixation point. Each run comprised blocks of 12 stimuli, 8 of 1 type and 4 drawn at random from the other 3 types to maintain expectancy. The four types were left hemifield-large letter, left hemifield-small display with flankers, right hemifield-large letter, and right hemifield-small display with flankers (Fig. 1). The order of runs was counterbalanced across subjects. Each run began with a 24-s period of blank, the 12 stimuli were presented at 2-s intervals (total stimulus block time = 24 s), and there was a rest interval of 24 s between each block of 12 stimuli while the screen was

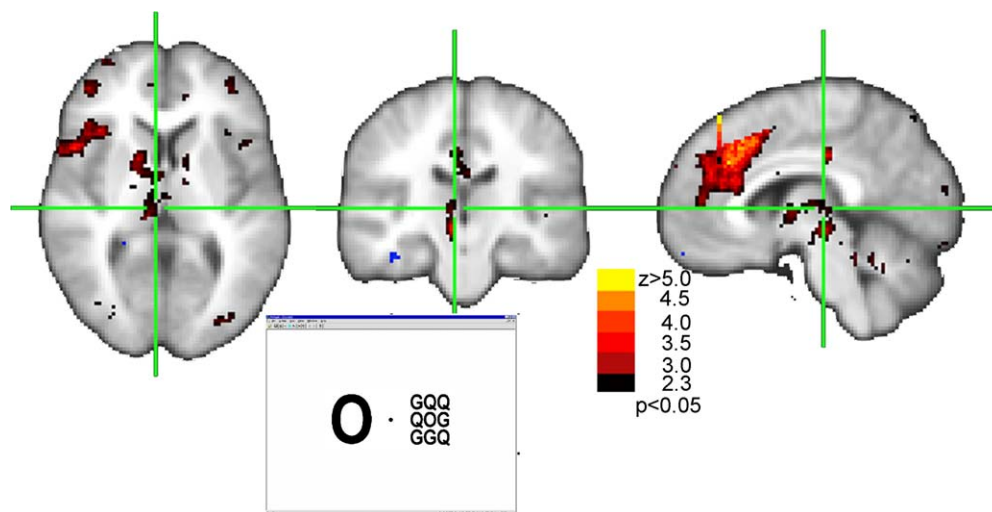


Fig. 1. Detection of small letter “o” surrounded by flanking small distracters (termed “SMALL”) associated with larger BOLD signal than detection of big letter “O” without flankers (termed “BIG”). Color bar indicates  $z$  score for each area. Note activity in MDN and pulvinar region of the thalamus, posterior and dorsolateral frontal lobe, and the cingulate gyrus. Threshold  $z = 2.33$ , for replication of earlier results [21]. Stimulus display elements: (inset) either right hemifield (RH) or left hemifield (LH) display is presented on any one trial. Hemifield of presentation for large or flanker-surrounded small letter is randomized.

gray and a fixation point appeared. Throughout the experiment, subjects had to visually fixate a dot corresponding to the center of the screen. The target could be a small letter O surrounded by flankers top or a big letter O presented alone. In half of the trials, the letter C or the digit zero 0 was presented as a distracter. The stimulus appeared alone as a big character or as a small character surrounded by eight other letters (Fig. 1). The letters were displayed in Arial typeface, and the overall size of the stimuli was controlled so that the big letters were of the same dimensions as the pattern of small letters surrounded by flankers, i.e., for “0” or “O” 19 or 22 mm wide. The subject’s task was to click on a standard mouse button (modified for use with MRI) each time he detected the letter O, either alone or surrounded by small letters, to ignore the C and the 0, and to press on the right button for a right-sided target and the left button for a left-sided target. Each display was flashed for 150 ms; with the 2-s interstimulus interval, this left 47.850 s to the next target.

Data analysis was carried out using FMRI Expert Analysis Tool (FEAT), Version 5.00, part of FSL (FMRIB’s Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). The following pre-processing

was applied; motion correction using MCFLIRT [16]; non-brain removal using BET [33]; spatial smoothing using a Gaussian kernel of FWHM 3 mm; mean-based intensity normalization of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with  $\sigma = 50.0$  s). Time-series analysis used FMRIB’s Improved Linear Model (FILM) with local autocorrelation correction [35]. Contrasts were computed to test for differences between BIG/SMALL and LEFT/RIGHT task conditions. The resultant Z (Gaussianised T/F) statistical images were thresholded using clusters determined by  $Z > 2.3$  and a cluster significance threshold of  $p = 0.01$  (corrected for multiple comparisons) [9,10,36]. Registration to high-resolution and standard images was carried out using FLIRT [16]. Multi-subject (higher level) analysis was carried out using FMRIB’s Local Analysis of Mixed Effects (FLAME).

Analysis of functional connectivity between seeds placed in the thalamus and all other brain regions was done in the programming language R. Talairach coordinates, placed in the center of the pulvinar, MDN and anterior thalamus, were selected a pri-

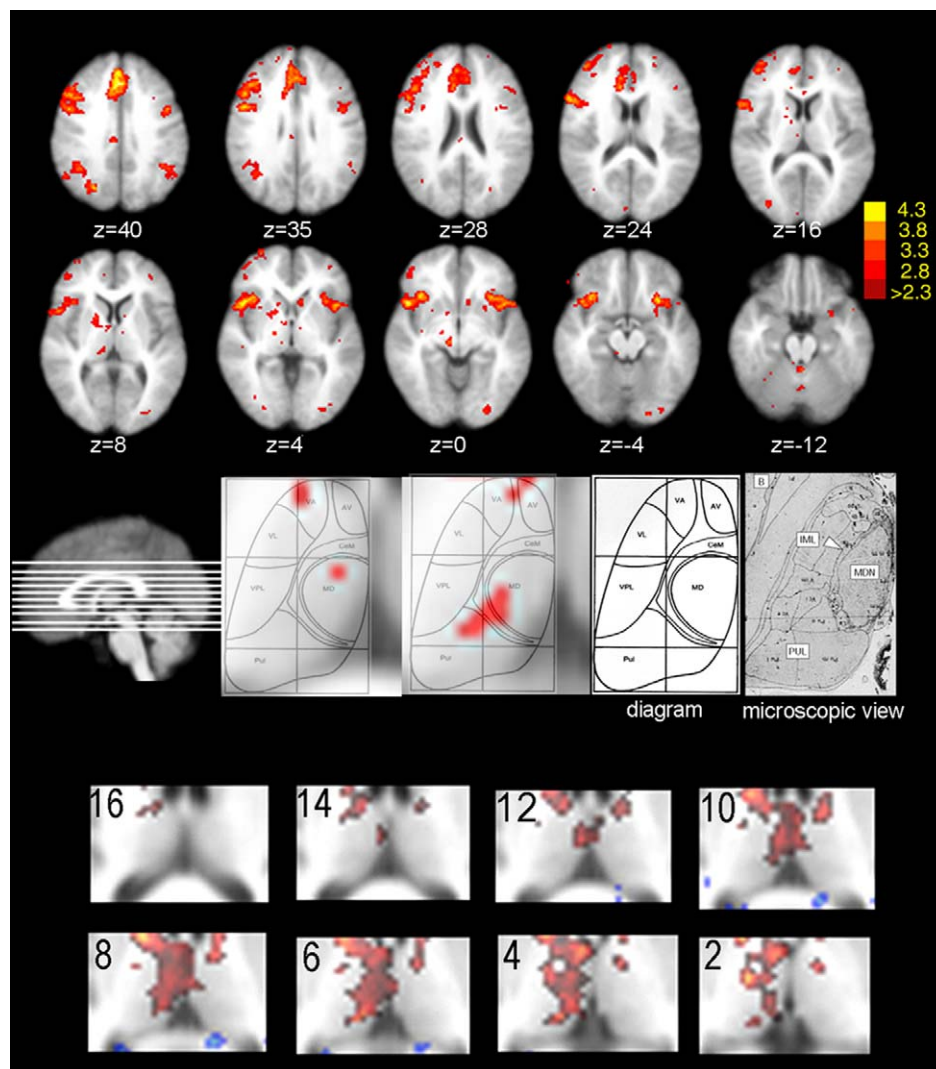


Fig. 2. Upper panel: small letters with flankers show greater BOLD response than large letters, corrected significance level,  $z = 2.33$ ,  $p < 0.01$ . Lower panel: close view of thalamus with anterior thalamus activated at  $z = 16$ , MDN on right at  $z = 14$ , and bilaterally below. Pulvinar activated more ventrally at  $z = 8$ – $2$ .

ori by a neuratomist. A random-effects analysis of covariance was carried on the beta coefficients from the first level analyses for the SMALL > BIG contrast, with the seed entering as an independent variable and all other voxels entering (on a voxel-by-voxel basis) as the dependent variable. This analysis shows the run-to-run (4 runs/person, 16 persons) covariance between the seed values and the values of all other voxels; it is thus a measure of intrasubject regional covariation. Because “subject” was modeled as a random effect, inferences can be drawn with respect to the population of subjects.

**Attentional effects of surrounding flankers:** As anticipated, BOLD signal was enhanced in the pulvinar in the BIG (single letter) versus SMALL (surrounded by flankers) condition. Enhanced activity (Figs. 1 and 2) was also marked in the anterior and superior cingulate (BA24 and BA24'), in the dorsolateral PFC, and in the frontal operculum and insula (Table 1). General involvement of the thalamus is seen in the sagittal view (Fig. 1). Anterior activation falls in the ventral anterior nucleus, and posterior activation in both the MDN and pulvinar. The pulvinar is activated in its ventral and medial portion (Fig. 2, bottom panel,  $z = 8$ ).

**Correlations with the MDN:** Expected correlations with bilateral dorsolateral PFC were observed (bottom panel, Fig. 3) and survived  $t = 5$  exploration and  $t = 2.33$  ( $p < 0.01$ ) confirmation (Figs. 3 and 4). Correlations also emerged with superior parietal and superior temporal cortex, as well as posterior cingulate.

Table 1

Regions of difference for small letter &gt; big letter response

Structure	x	y	z	Maximum t
Pulvinar	−12	−32	6	2.92
Anterior thalamus	−6	−8	2	2.92
Anterior cingulate	0	26	34	4.97
Superior parietal lobe	−38	−52	34	3.22
Dorsolateral-prefrontal	−48	14	34	4.38
Dorsolateral-prefrontal	44	10	2	4.32
Inferior parietal	−24	−74	40	2.92
Insula	−46	12	0	4.43

**Correlations with pulvinar:** We first evaluated the hypothesized areas—parietal lobe for the pulvinar, dorsolateral PFC for the MDN, and cingulate for the anterior nucleus. For the pulvinar, the area of highest correlation of the BOLD small letter > big letter effect was the parietal lobe, BA39 (Figs. 3 and 4). Correlation with the hippocampus, medial geniculate, and possibly the superior colliculus is also seen. Little correlation was found with areas in the temporal lobe.

**Correlations with anterior thalamus:** For the anterior thalamus, the highest functional connectivity was with the anterior cingulate, but also with posterior cingulate and dorsolateral PFC.

These results confirm and extend our earlier findings of activation of the pulvinar during visual target detection with spatial

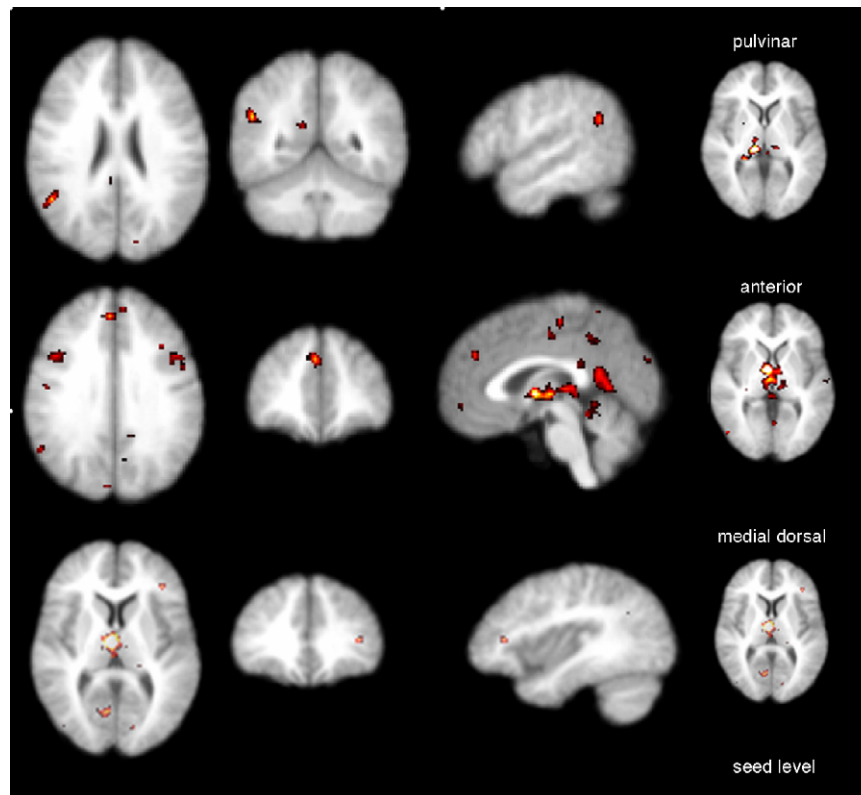


Fig. 3. Seed correlations. Top row: correlations with pulvinar in axial, coronal, and sagittal planes with seed level slice on right. Correlation is maximal with seed area (with itself) and its own region in the opposite hemisphere. For the pulvinar, the maximum correlation is with BA39 in the parietal lobe. Middle row: correlations with the anterior thalamus. For the anterior thalamus, the correlation is maximal in the anterior cingulate, but significant areas are also found in frontal lobe (BA8) and in posterior cingulate. Bottom row: correlations with MDN. The correlation is maximum in the dorsolateral prefrontal region (Talairach xyz, 38, 30, 8; inferior frontal cortex, BA45/46). Threshold is  $t = 5.0$  for exploratory presentation.



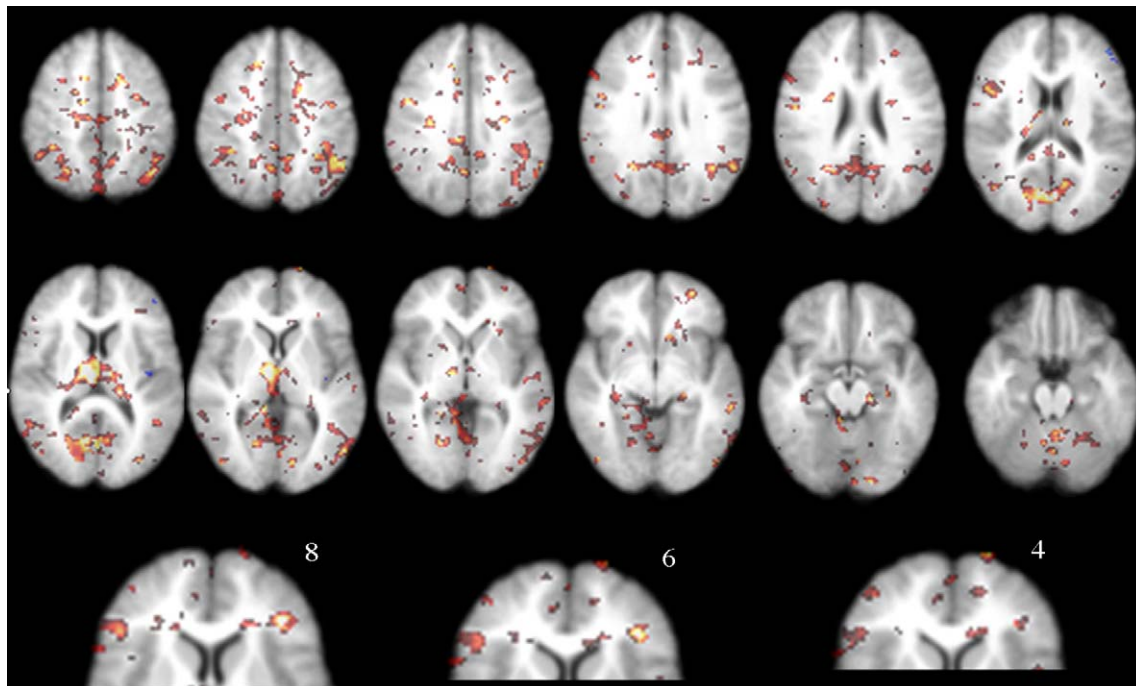


Fig. 4. Correlations of BOLD activity with seed pixel in MDN. Top two rows: images at  $z = 52, 42, 38, 32, 26, 18, 12, 4, 0, -6, -14, -20$  to represent thalamic region at closer intervals than dorsal cortex,  $t = 3.28, p < 0.0025$ . Bottom row: enlargement of frontal region to show pattern of dorsolateral correlation with  $t = 2.3, p = 0.01$ .

distracters. Here we examined the correlated cortical areas and found patterns of distinctive but widespread reciprocal association for the MDN, pulvinar, and anterior nucleus. It must be emphasized that *correlation* is not direct evidence of *connection*, but rather of regional *covariation* common across individuals. Correlations can arise from the effects of direct connection as well as the effects of connection with a third, possibly unidentified structure or network. Very small structures with highly divergent projections might be underrepresented and missed as intermediate circuit links. Correlations might also arise from similarity in feature detection (e.g., high versus low spatial frequency mechanisms) or histological qualities present in multiple cortical areas. The possibility of false-positive results with significance probability mapping must also be considered. Pulvinar activation was expected based on our earlier PET study with the same task [21], and therefore a  $t = 2.33$  appeared indicated; it would be a weak disconfirmation to report that our earlier result was not confirmed with new results that met a  $p < 0.05$  threshold. Hypotheses about the posterior parietal lobe [27,37], superior colliculus [27], inferior temporal lobe, anterior cingulate gyrus [37], and prefrontal regions have been proposed, and there are existing fMRI thalamus-versus-cortex correlations reported in the literature, so it appeared biased to consider our own findings at a  $p < 0.05$  level but hold all other investigators' theories and findings to require  $p < 0.01$  or higher. Cluster-corrected (for multiple comparisons) whole brain maps are therefore provided for examination. For seed correlations, the presentation was more exploratory and required  $t = 5$  to screen the findings, but  $t = 2.6$  ( $p < 0.01$ ) are also presented to show the expected PFC-MDN correlations. Two levels of thresholding for important maps are presented together with a  $p$ -value color bar so that readers with different anatomical connection data or differing fMRI results

can consider the data in the context of their own view of what is exploratory and what is confirmatory.

Lack of temporal but not right parietal lobe activation is consistent with our interpretation [21] that the task is not a language task involving names and verbal processing of letters but a visual perception task involving spatial focusing of attention. Our pulvinar-versus-temporal lobe correlations were also minimal and not as strong as the MDN correlations. FDG-PET correlations calculated across individuals indicated both dorsomedial and pulvinar correlations with temporal regions [24]; this difference may reflect the use of a memory-activation task or the examination of inter-individual rather than intra-individual correlations. A structural equation modeling analysis of a flanker task proposed and confirmed a model very close to our more exploratory results: thalamus, PFC and parietal cortex have significant path coefficients [8]. Correlations between the PET dopamine<sub>2</sub>-receptor ligand FLB457 in the thalamus and frontal or temporal lobe were not significant in normal subjects [38].

The anatomy of pulvinar projections suggests functional cortico-thalamo-cortical loops involved in a variety of functions including salience, attention and working memory [13]. Such loops could function in one of two ways. Most medial pulvinar neurons are posited to project back to the same cortex from which they receive input [13]. Thus, each medial pulvinar unit might signal salience only to its own cortical fields. Alternatively, open-loop connections could be used to pass information from one cortical field to another, perhaps from lower (e.g., sensory) areas to areas of more complexity. The anterior, medial and lateral regions of the pulvinar not only have visual projections but also projections to the superior temporal gyrus, which has connections to prefrontal cortical regions that project recipro-

cally to both the MDN and the pulvinar [25]. Our data showed greater MDN correlation with superior temporal gyrus than pulvinar correlation; this might represent association of both areas with parietal areas, or greater individual differences in exactly which areas of the superior temporal lobe are used in this task.

These correlation analyses confirm the functional connectivity between the MDN and prefrontal regions seen in other connectivity studies [24] and are consistent with neuroanatomical studies demonstrating dorsomedial/prefrontal connectivity. Detailed exploration across tasks that recruit temporal and parietal areas as well as prefrontal participation will be a useful next step.

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