

Changes in functional connectivity of human MT/V5 with visual motion input

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The neural basis of human mental function is characterized by interactions between brain regions. Temporal correlations in MR signals between areas may provide one method for investigating these interactions. This approach was used to examine functional connectivity in the motion processing system of the human brain. Correlations between MT/V5 and other brain regions were examined in a resting state (without visual stimulation) and in an active

state produced by viewing moving concentric circles. A network of regions consistent with the known functional anatomy of visual processing was correlated with MT/V5 during rest. When subjects were viewing motion, a more limited network was correlated with MT/V5, suggesting MT/V5 was acting in concert with a smaller network specific to the task. *NeuroReport* 15:1315–1319 © 2004 Lippincott Williams & Wilkins.

Key words: fMRI; Functional connectivity; Low-frequency correlation; Middle occipital gyrus; MT; Neuroimaging; V5; Visual motion

INTRODUCTION

fMRI studies have previously examined the temporal correlations in BOLD signals from separate brain regions as a surrogate measure of inter-regional connectivity. Such studies use inter-regional correlations to investigate how different neural regions orchestrate their activity to perform different cognitive operations. One approach examines inter-regional synchrony during so-called steady states, such as during resting scans, or scans obtained during continuous task performance. The correlations between low frequency signal variations have been found to reflect patterns of known connectivity in motor, auditory, visual, limbic, working memory, and language systems [1–5]. Recent studies have revealed differences in inter-regional resting correlations in patients with multiple sclerosis [6] and with agenesis of the corpus callosum [7], also supporting the view that these correlations are related to inter-regional connectivity.

Other studies have examined such correlations during continuous task performance with mixed results. A study of correlations to dorsolateral prefrontal cortex found that this region had greater correlations with a network of working memory regions during performance of a working memory task and greater correlations with motor regions during a finger tapping task [4], suggesting that steady-state inter-regional correlations are indicative of the different functional interactions between regions during the performance of different tasks. Similarly, a study examining steady-state correlations between language areas also found that correlations between regions in the language circuit were

greater when subjects were performing a continuous receptive language task than when subjects were resting [3]. On the other hand, correlations between motor cortex and other motor regions did not increase during performance of a finger tapping task as compared to rest [8]. It may be that motor regions are strongly coupled even when no motor tasks are being performed, whereas connections are weak between regions involved in cognitive tasks until the cognitive circuit is activated. Although resting correlations have been compared with steady-state task correlations for both cognitive and motor tasks, to our knowledge there has been no study to date comparing correlations between sensory processing areas at rest and during a sensory task.

Here we report our measurements of resting and task-related correlations in MR signals to a well-studied visual processing region: middle temporal area (MT/V5). Studies in non-human primates have shown that cells in MT respond to moving stimuli [9]. fMRI and PET studies have identified an area with similar response properties located in the temporo-parieto-occipital junction in humans [10–12]. This motion-sensitive region, referred to as human MT/V5, has been agreed to be homologous to macaque MT on the basis of its responsiveness to motion, not its anatomical location.

Although the anatomical connectivity of human MT/V5 is not known precisely, connectivity in the primate visual system has been mapped extensively. In the macaque, MT has reciprocal connections with the visual cortical areas V1, V2, V3, VP and V4, as well as some higher level areas (MST,

VIP), and with subcortical regions including the caudate, the claustrum, the putamen, and several thalamic nuclei [13]. The human analogue of V1 lies along the calcarine sulcus. V2 wraps in a horse-shoe shape around V1, with its lower parts on the lingual gyrus [14]. Analogues of VP and V4 can be found ventrally, and an analogue of V3 dorsally [15]. However, care must be taken in assuming that connectivity between regions in the macaque will be identical to connectivity between the analogous human regions, as these regions do exhibit functional differences. For example, in humans, V3A is more motion sensitive than V3, while the reverse holds in the macaque [16]. Thus it is possible that MT may be less connected to V3 and more connected to V3A in humans relative to the macaque.

Functional activation studies can also provide clues to the connectivity of human MT/V5. Human MT/V5 has been found to activate along with other visual areas to a wide range of visual processing tasks. Depending on the specific stimuli and task, other visual areas activated have included the calcarine sulcus, lingual gyrus, middle occipital gyrus, and portions of the cuneus [10,17]. In this study, functional connectivity between MT/V5 and these visual areas is examined both at rest and during continuous viewing of a display of outwardly moving concentric circles.

MATERIALS AND METHODS

Two experiments with different slice acquisitions were conducted, each composed of two parts: a traditional block-design motion processing paradigm (2 runs) and functional connectivity runs in which subjects rested for entire runs (2 runs) or in which subjects viewed moving circles for entire runs (2 runs). The first part was used to identify a reference motion processing region (MT/V5) for the correlations computed in the second. In the functional connectivity runs, data from the steady state scans were used to create maps of functional connectivity to that reference region in each condition (resting and viewing motion).

Subjects: In experiment 1 four males and three females were tested; one male and five females were tested in experiment 2. All subjects gave informed consent in accordance with a protocol reviewed and approved by the Human Investigations Committee of Yale School of Medicine.

Experimental paradigm: In the first part, motion localizer moving concentric ring stimuli were used to identify the human homologue of primate MT/V5. The stimuli consisted of two interleaved conditions (in 24 s blocks): outward moving low-contrast concentric rings (subtending 17° angle, frequency 2.5 Hz) or static concentric rings in which a single frame was continuously present. Subjects were instructed to maintain fixation on the center of the rings.

In the second part, in which correlation maps were defined, the time course of signal from the localized MT/V5 region was used as a reference signal to determine which brain areas showed correlated patterns of activity during rest (with eyes closed) and in the motion condition (viewing outwardly expanding rings, fixating on center). These expanding concentric circles were presented at the same frequency and intensity as used for the localizer. Subjects

were instructed to keep their eyes focused on the center of the display.

Data acquisition: Subjects were scanned in a GE 1.5T Signa LX scanner. In experiment 1, scanning sessions began with the acquisition of sagittal localizing slices. This was followed by the acquisition of nine contiguous 7 mm thick axial T1-weighted images for anatomical identification (TR=500 ms, TE=14 ms, FOV=20 × 20 cm, 256 × 192 acquisition matrix).

Each functional run involved the acquisition of 340 images for each of the nine slices (prescribed in the same locations as the anatomical data). A T2*-sensitive gradient-recalled, single shot echo-planar pulse sequence was used for acquisition of these functional images (TR = 1000 ms, TE = 50 ms, flip angle = 60°, FOV = 20 × 20 cm, and a 64 × 64 acquisition matrix). The first 10 images taken in each scanning run were discarded, and the remaining 330 images per slice were used for analysis.

Data acquisition in experiment 2 was identical to that for experiment 1 except that 16 contiguous 7 mm thick axial slices were collected in the anatomical and functional runs, to allow examination of dorsal regions of the brain. This required an adjustment of parameters in the functional imaging runs to TR = 1500 ms, TE = 50 ms and flip angle = 80°.

Data analysis: All data were motion corrected using the SPM99 algorithm (<http://www.fil.ion.ucl.ac.uk/spm/>). Activation maps and composite analyses were computed using software developed in our laboratory in MatLab by Dr Pawel Skudlarski (<http://mri.med.yale.edu/individual/pawel/fMRIpackage.html>).

For the localizer runs in the first experiment linear drifts in signal were removed [18] and images were assigned to still or moving blocks (after adjusting for hemodynamic lag). A pixel-wise, two sample *t*-test was performed, comparing each pixel's signal level while viewing the expanding circles to its signal level while viewing the stationary circles. The MT/V5 region was defined for each subject based on their individual activation map. T-maps were thresholded at $t = 2$ and cluster filtered to remove any pixels that did not have at least 2 neighbours active. MT/V5 was then defined to include all remaining activated pixels in, or adjacent to, the temporo-parieto-occipital junction, as identified based on anatomical landmarks and Talairach coordinates.

Maps of the percentage signal change between the moving and still blocks were also computed for each subject and transformed into Talairach coordinates. For each pixel in the standardized Talairach maps, a *t*-test was performed comparing the 13 values of that pixel obtained across subjects to zero. This yielded a composite map of statistical significance. Those slices of this composite map that contain data from all 13 subjects are displayed with a cutoff of $p < 0.001$ after cluster filtering to remove any activations involving < 10 contiguous pixels.

In the second experiment, low-frequency (< 0.1 Hz) temporal correlations with the signal from MT/V5 were computed in the resting data of each subject following the procedure of Hampson *et al.* [3]. To summarize, the data from each run were low-pass filtered (see [1,4,5]). Then, for each run, the partial correlation between the timecourse of

each pixel and that of MT/V5 was found, after removing the effect of the global timecourse. These correlations were averaged across runs and transformed to an approximately Gaussian distribution via Fisher's transformation. By fitting the distribution with a Gaussian and adjusting for mean and standard deviation, the data were then transformed to a standard normal distribution [5]. This yielded a map representing the strength of resting state correlations to MT/V5 in terms of standardized z-values.

An identical analysis was applied to the data from the runs in which subjects viewed the continuously moving circles to obtain a map representing the strength of correlations to MT/V5 during the motion task in terms of standardized z-values.

The z-maps computed from resting data for each subject were transformed to Talairach coordinates. Data were averaged across the standardized z-maps in each experimental group. The resulting average maps were not intended to determine statistical significance, but to allow visual inspection of the results from the separate groups. Using the data from all 13 subjects (i.e. combining data from the two experiments), a *t*-test was performed on each pixel of the Talairach maps to produce a composite map of the statistical significance of resting state correlations with MT/V5. Similarly, the z-maps of cross-correlations during continuous visual motion processing were transformed to Talairach coordinates and combined across subjects to produce a composite map of correlations with MT/V5. Maps were cluster-filtered to remove activations <15 contiguous pixels.

RESULTS

Visual motion processing activated a typical set of brain regions in all subjects. A region in the temporo-parieto-occipital junction corresponding to MT/V5 was strongly activated as expected, allowing functional definition of a region for each subject that could be used as the reference region in the correlation analyses. The middle occipital gyrus just posterior to MT/V5 was also significantly activated by the motion processing task (Fig. 1; Table 1).

Combined correlation results (statistical maps): Maps showing correlations to MT/V5 in Exp. 1 and 2 separately

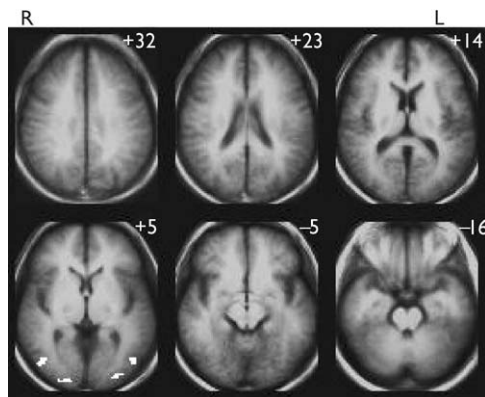


Fig. 1. Composite statistical map (experiments 1 and 2) of brain activation in response to motion localizer. Results are shown in Talairach space at a threshold of $p < 0.001$. Z-coordinates are shown in upper right corner of each slice. Positive activations are white, negative are black.

Table 1. Talairach coordinates in the x, y, and z planes for regions showing significant activation to motion localizer (column 1) or correlation to MT/V5 (columns 2&3).

Activation site	1. Motion localizer	2. Resting correlations	3. Motion correlations
MT/v5 (L)	-45, -68,5	-43, -67,8	-45, -72,5
MT/v5 (R)	42, -69,5	44, -67,5	44, -65,6
MOG (L)	-29, -85,5	-29, -84,5	-28, -83,5
MOG (R)	20, -90,5	32, -80,5	33, -80,9
LG (L)	—	-18, -67,5	—
LG (R)	—	20, -58,5	—
Thalamus	—	-2, -14,14	—
Cuneus	—	5, -82,23	—

MOG: Middle occipital gyrus, LG: lingual gyrus, R: right hemisphere, L: left hemisphere.

are available at <http://mri.med.yale.edu/individual/Hampson/correlationfigures.html>. Findings from both experiments were similar and are captured in the statistical composite map computed across all subjects (Fig. 2). In the resting state, there were strong correlations between MT/V5 and a network of visual areas including parts of the middle occipital gyrus, the cuneus and lingual gyrus, as well as an inverse correlation with the thalamus (see Table 1 for coordinates). In the motion processing runs, correlations to the cuneus, lingual gyrus and thalamus decreased significantly in magnitude while correlations to the middle occipital gyrus remained strong.

DISCUSSION

Low-frequency resting state correlations revealed a network of areas functionally connected with MT/V5. This network included the thalamus, a dorsal portion of the cuneus, lingual gyrus, and middle occipital gyrus. These findings are consistent with other imaging studies that have reported MT/V5 to be activated in concert with many of these early visual processing regions for a variety of visual tasks, including various forms of visual motion processing [17,19]. Activations in similar areas of the lingual gyrus and cuneus have been suggested to correspond to V2/Vp and V3/V3A, respectively [17]. Thus, the regions found to be correlated with human MT/V5 during rest appear to be consistent with known anatomical connectivity between analogous visual regions in the macaque [13].

When participants viewed continuous motion, the functional connectivity between MT/V5 and the dorsal cuneus, lingual gyrus, and thalamus decreased in magnitude. Correlations with middle occipital gyrus, however, remained strong. The middle occipital gyrus, an area tightly coupled with MT/V5 in motion processing, is often co-activated during visual motion processing [19,20]. Activations very near the locus of the middle occipital gyrus peak reported here have been found in many visual motion studies but given different names, including human V3A [21], functionally defined human kinetic occipital area (KO) [22], and V3B [23]. Regardless of name, it appears that this region is an important component of the human visual motion processing system. The regions activating in response to the visual motion display during the localizer runs (Fig. 1) also included the middle occipital gyrus but did not include the cuneus, the thalamus or the lingual gyrus. This supports the interpretation that the less

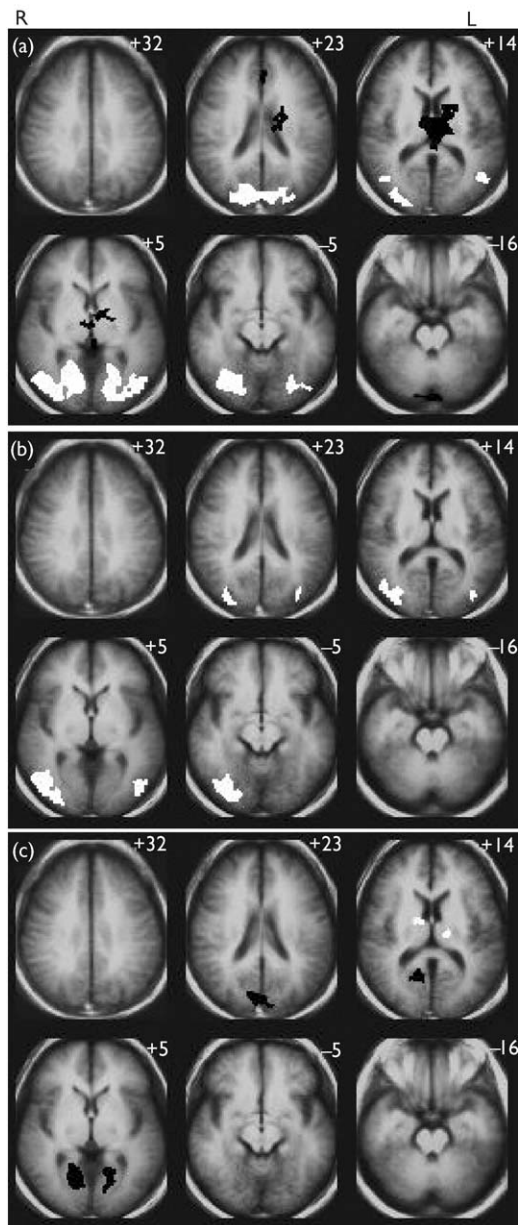


Fig. 2. Composite statistical map (experiments 1 and 2) of correlations to MT/V5. Results shown in Talairach space at a threshold of $p < 0.001$. (a) Resting; (b) motion processing; (c) motion processing – resting. Z-co-ordinates are shown in upper right corner of each slice. Positive activations are white, negative are black.

extensive correlations to MT/V5 reflect the activation of a smaller network during this specific motion task.

Explanations for the decreased correlations measured during the motion processing task are mainly speculative. However, it should be noted that the resting and active states differ not only because of the presence of a sensory stimulus, but also because in the active state the subject is attending to the task. Attention to visual motion has been shown to affect the activity of V5 and V3A [24]. As pointed out by Friston and Buchel [25], neuronal responses in sensory areas may reflect an interaction between bottom up driving afferents from lower cortical areas and backwards modulatory inputs from higher areas. In particular, they

reported modulation of responses in V5/MT from parietal regions involved in selective attention and proposed these regions modulate the effective connectivity from early visual cortex to the motion-sensitive area V5/MT. They found that backwards modulatory influences from the posterior parietal cortex may account for a significant attentional modulation of V5/MT responses to driving inputs from V2. The possible role of such interactions need to be considered in further studies of correlational effects as measured using steady state designs.

Although accumulating evidence suggests that correlations between regions can be used to identify functionally connected circuits, care must be taken in the interpretation of such data. In particular, it remains to be established whether these correlations provide information regarding the internal structure of circuits. If correlations between regions arise because of some phase locking mechanism that synchronizes the blood flow patterns between regions with strong neural connections, then the strength of the correlations may provide information regarding the strength of the corresponding connections. In this case, inter-regional correlations may provide complementary information to activation maps. However, if inter-regional correlations arise between functionally related regions because a functional circuit (as a whole) varies in the degree of its activation, then no conclusions may be drawn regarding the internal structure of these circuits based on the correlations. In the latter case, the correlations may still provide information regarding the set of regions comprising the circuit. A greater understanding of the basis of these correlations is needed to guide our interpretation of functional connectivity measurements.

CONCLUSION

Functional connectivity of the human homologue of motion processing area MT/V5 was studied by examining low-frequency correlations in data collected at rest and while viewing motion. The resting state correlations revealed a broad network of correlated regions that were in good agreement with known functional pathways for general visual processing, whereas the active state correlations revealed a more specific network of regions that appear to work in concert for this specific visual motion processing task. We suggest that there is a broad network of regions connected to area MT/V5 and that the individual regions in this network, depending on the particular type of motion or task demands, will or will not be co-activated with MT/V5.

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