Differential Functional Connectivity of Prefrontal and Medial Temporal Cortices During Episodic Memory Retrieval

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Abstract: Some theories of brain function emphasize the interactions between brain areas as the major determinant of cognitive and behavioral operations. We explored such interactions in a PET study of episodic memory retrieval having three retrieval conditions, with differing levels of retrieval success. Functional connectivity of voxels located within Brodmann areas 10 and 45/47 in the right prefrontal cortex (RPFC) and the left hippocampus (LGH) with the rest of the brain was estimated using partial least squares. Area 10 and LGH showed an opposite pattern of functional connectivity, with a large expanse of bilateral limbic cortices that was equivalent in all tasks. However, during high retrieval, area 45/47 was included in this pattern. The results suggest that activity in portions of the RPFC reflects either memory retrieval mode or retrieval success, depending on other brain regions to which it is functionally linked. *Hum. Brain Mapping 5:323–327, 1997.* © 1997 Wiley-Liss, Inc.

Key words: covariance; positron emission tomography; regional cerebral blood flow; human; neuroimaging; neural networks; hippocampus

INTRODUCTION

In neuroimaging studies of human memory, one of the most reliable activations is that of the right prefrontal cortex (RPFC) during episodic memory retrieval [Tulving et al., 1994; Cabeza and Nyberg, 1997]. Experiments following from this observation suggest that the activation of RPFC may reflect ''retrieval mode,'' or the act of searching without regard to the success of this search [Nyberg et al., 1995]. When RPFC activity is considered in isolation, this classification may be reasonable. However, the role a region plays in cogni-

tion may be determined through the coordination of several interconnected brain regions rather than by some intrinsic property of that area [McIntosh and Gonzalez-Lima, 1994; McIntosh et al., 1996a]. Thus it is possible for the RPFC to be related to both retrieval mode and retrieval success depending on its interactions with other brain areas. Is retrieval mode best represented solely by the activation of RPFC, or are there several networks, differentially engaged, whose influences result in a similar pattern of activations, all labeled retrieval mode?

One way to examine whether the same region has a consistent pattern of interactions across retrieval tasks is to explore change in ''functional connectivity,'' loosely defined as the correlation of activity among brain regions [Gerstein et al., 1978; Friston, 1994]. The neurobiological interpretation of functional connectivity is

simply that two or more regions show correlated activity without reference to how the patterns may be mediated [Friston, 1994]. Further elaboration requires more explicit models to determine the effect regions have on one another, or "effective connectivity" (further discussion can be found in Friston [1994] and McIntosh and Gonzalez-Lima [1994]). However, functional connectivity can be used to address simple questions regarding the association of regions during a particular cognitive operation. For example, in the present case, if retrieval mode is best represented by the same neural system, then the pattern of functional connectivity between RPFC and the rest of the brain should show similarities across memory retrieval tasks; otherwise it is likely that different systems are engaged, all of which include RPFC, that lead to similar patterns of activity.

MATERIALS AND METHODS

Data set

Data for this application came from a PET regional cerebral blood flow (rCBF) study of episodic memory retrieval [Nyberg et al., 1995, 1996]. The purpose was to establish whether the act of memory retrieval (i.e., retrieval mode) yielded a common pattern of activity independent of retrieval success. Three retrieval tasks were used with differing levels of retrieval success. Before scanning, subjects (n = 11, age range 24–31 years) were presented with two lists of words, some spoken by a male and some by a female. For one list, subjects were asked to identify the gender of the speaker (shallow processing), and for the other list they were asked to decide whether the word represented a living thing (deep processing or semantic encoding). The retrieval conditions consisted of yes/no recognition (indicated by a button-press) for visually presented word lists that were either: 1) all unstudied (New), 2) from the shallow processing list (Shallow), or 3) from the deep processing list (Deep). Retrieval success would be highest in condition 3, but in all tasks subjects would be in retrieval mode. A baseline task was also done, where a subject read a single word and pressed a button. Each condition was scanned twice.

Regional activations

Activation analysis was performed using partial least squares (PLS) [McIntosh et al., 1996b].[1] The

strongest pattern of activity identified by PLS differentiated all three retrieval conditions from baseline (permutation test, $P < .001$). Areas commonly activated during the retrieval tasks were in two parts of the right inferior prefrontal cortex (area 45/47, Talairach and Tournoux [1988] coordinates: X = 32, Y = 22, Z = 0, and area 10, X = 28, Y = 44, Z = 4), left anterior cingulate (area 24, X = −14, Y = 20, Z = 32), left ventral occipital cortex (area 18, X = −18, Y = −100, Z = −16), and cerebellum (X = −38, Y = −82, Z = −28). Deactivated areas included the bilateral temporal areas (area 20, X = 50, Y = −28, Z = −24; X = −60, Y = −10, Z = −16), left middle frontal (area 8/9, X = −34, Y = 26, Z = 40), right medial frontal (area 10, X = 6, Y = 52, Z = 8), and posterior cingulate cortices (area 23, X = 0, Y = −54, Z = 16). The left hippocampal gyrus (LGH, X = −24, Y = −36, Z = −8) was identified as the dominant area in a pattern of activity that distinguished Deep from all other tasks [Nyberg et al., 1996]. Unlike the RPFC, the LGH activation was unique to one retrieval task, implying strong involvement with successful retrieval.

For analysis of functional connectivity, representative voxels from three areas were selected: the two RPFC areas and the LGH. The RPFC regions, assuming their activation reflects retrieval mode, should have shown common patterns of connectivity across the three retrieval conditions, while the LGH, which may be more related to retrieval success, should have shown a pattern of connectivity unique to the Deep condition. It should be emphasized that the area designations (area 10 and area 45/47) are meant only as guides to approximate location and are not meant to imply that the entire cortical area represented is functionally homogeneous. Indeed, the results would likely be quite different if different locations within the same Brodmann designation were used.

Partial least squares analysis

The conceptual description of the PLS procedure used to analyze functional connectivity is most easily understood as an extension of a "seed voxel" correlation analysis proposed by Horwitz et al. [1992]. The procedure produces a statistical map of areas that are correlated with a location of interest (the seed voxel). The maps may then be compared between tasks to ascertain any experimental changes in correlation pat-

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[1]The coordinates for some of these peaks are slightly different than in the original report [Nyberg et al., 1995] owing to the fact that we

used a smaller smoothing filter for the present investigation (10 mm vs. 15 mm). The right frontal peak was originally reported as a single large area, but with the smaller filter it separated into two spatially distinct regions.

terns. The seed correlation procedure may become somewhat cumbersome when there are several tasks and several voxels to consider. This is where PLS can provide some assistance. Analysis of these correlation maps with PLS simultaneously provides a new set of maps that may represent areas showing common correlation patterns, on the one hand, and correlation patterns that show systematic task-related changes on the other. Put another way, PLS sorts the correlations into what is the same and what is different across tasks.

A full description of PLS in the neuroimaging context has been published elsewhere [McIntosh et al., 1996b]; here we describe modifications of the method to address issues of functional connectivity. The procedure is basically the same as the PLS analysis of brain-behavior relations. At the outset, voxel counts from repeated scans (within subjects within task) were averaged. A representative voxel value was selected for each of the three regions of interest, and within each task the covariances of these voxels were computed with all the voxels of the original image, save for the covariance of the seed voxel with itself. There results a matrix of covariances, 12 columns by about 60,000 rows (the number of voxels in an image volume that are measuring brain activity), with each column representing a within-task correlation map for a seed voxel.

A singular-value decomposition of this crossblock covariance matrix results in 12 latent variable (LV) pairs. Each pair accounts for progressively less of the summed squared crossblock covariance (SSCC), a rough index of importance. Each LV pair combines one profile of 12 entries over seed voxels and tasks with another profile, *the singular image,* over voxels of the whole image. The singular image optimally covaries with the seed voxel-task profile, and vice versa. The inferential significance of a latent variable is assessed through permutation tests [McIntosh et al., 1996b].

In the present analysis, the singular image can be interpreted as a pattern of functional connectivity, with the seed voxel-task pattern indicating how strongly the whole image participates with the salient seed voxels and tasks given by the 12 profiles. For each singular image, the variation in saliences across seed voxels and tasks similarly identifies task-related commonalities or differences of relation to that singular image. Singular images of different LV pairs are geometrically orthogonal (that is, have a crossproduct of zero), and likewise the seed-task profiles of different LV pairs.
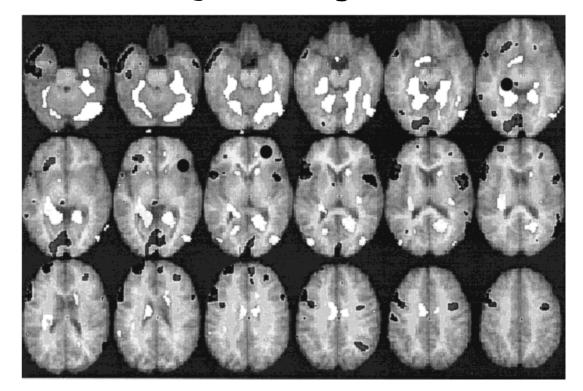
RESULTS AND DISCUSSION

Only the first four LVs from the PLS analysis were considered. Together they accounted for 83% of the

SSCC. The singular image from the first LV is displayed in Figure 1 (permutation, $P \ll 0.001$). Large areas of positive saliences extend across bilateral inferior temporal lobes, hippocampal and parahippocampal gyri, and retrosplenial cortex. Negative saliences are noted in left and right middle and dorsolateral prefrontal, medial occipital cortices, and midbrain. The first LV was mainly influenced by a common trend in covariances across seed voxels in LGH and area 10. There was, however, an interesting addition in the Deep condition. Along with LGH and area 10, the Deep condition showed a strong positive salience for right area 45/47. This area was not salient for any other task.

One may interpret this LV to suggest that there is a common pattern of covariances between right area 10, LGH, and the other limbic and frontal areas identified on the singular image. Interestingly, these areas showed opposite patterns of functional connectivity indicated by the opposing saliences. In the Deep condition, involving high memory retrieval following semantic encoding, another right prefrontal region, area 45/47, showed strong covariances with limbic areas. That is to say, these voxels are bound by a common pattern of functional connectivity only when there is successful episodic retrieval.

This interpretation of the profile of seed-task LV1 may seem incongruent with the results from the activation findings, which deal with mean differences, and not covariances of voxels. Recall that RPFC areas used here were relatively activated in all retrieval tasks, while the LGH was active only in the Deep condition, and that the covariance patterns of LGH and area 10 were fairly stable across tasks. Area 45/47, however, was only salient for the Deep condition. Patterns of covariation across the other three LVs (not presented graphically) suggested that the task-related activation of RPFC may not have arisen from the same functional connections. LV2 was expressed mainly for the Shallow and Deep conditions and was salient for the two right prefrontal regions (permutation, $P = 0.04$). The singular image on LV2 identified negative saliences in bilateral inferior temporal cortices and posterior cingulate. Interestingly, these regions were deactivated in the comparison of retrieval tasks to baseline. The third LV, which was not statistically significant, was expressed only for the reading baseline and was salient for right area 45/47 (permutation, $P = 0.2$). The singular image showed bilateral frontal polar cortex (area 10) and medial occipital cortex. The last LV was expressed for the New and Shallow tasks (permutation, $P = 0.012$). The salience for right area 45/47 was
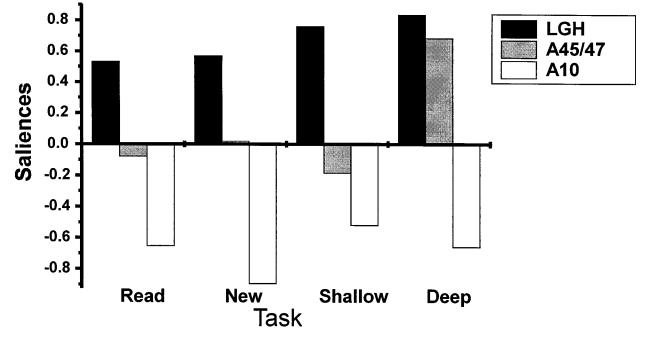
Singular Image LV1

Figure 1.

First latent variable from the PLS analysis of seed voxel correlations for left hippocampus (LGH), right Brodmann area 45/47, and right area 10. At bottom is a plot of saliences by seed voxel by task, indicating how strongly the voxel covaries by task with the singular image at top. This profile can be interpreted as the pattern of functional connectivity of LGH vs. A10 for three tasks, but LGH and A45/47 vs. A10 for the Deep condition. The singular image depicts covariances, voxel by voxel, with this contrast profile. Positive saliences (voxels with greater values for higher LGH values) are drawn in white, negative saliences (voxels with greater values for higher A10 values) in black, with both thresholded at a salience >0.5 (absolute value). The image is displayed on horizontal sections from a stylized MRI that conforms to the atlas space of Talairach and Tournoux [1988]. Slices start at −28 mm from the AC-PC line at the top left slice and move in increments of 4 mm to +40 mm at bottom right; left is left, and the top is anterior in the image. Black circles within the singular image mark the location of the three seed voxels and the surrounding voxels that were removed to reduce the spatial autocorrelation.

strong, and the singular image identified right parietal and medial prefrontal cortices.

The results from the PLS analysis suggest that similar patterns of activation can come about through different patterns of functional connectivity. Prefrontal area 10 and the LGH showed common correlations across all conditions for the present experiment, but only when there was high memory retrieval following semantic encoding was area 45/47 incorporated into the pattern. In light of the activation analysis, this may imply that the greater activation of the three seed voxels in the Deep condition arises through their common functional connections. For the Shallow and New tasks, however, the common activation of the two right prefrontal regions came about through other patterns of connectivity, perhaps due to increased suppressive influences on other regions (LV2) and stronger interactions with parietal and medial frontal regions (LV4).

In neuroimaging studies, patterns of activation identified through statistical analyses are often interpreted as reflecting a "distributed system" that subserves the cognitive operation of interest. However, explicit analysis of interactions may demonstrate that the same pattern of activations can be brought about by quite distinct interactions among systems. Explicit examination of neural interactions with structural equation modeling has substantiated this observation for prefrontal and anterior cingulate cortices [McIntosh et al., 1996a]. Congruent findings have also come from other multivariate analyses of PET data [Friston, 1994; Strother et al., 1995] and, together with the present study, support the general notion that a region may have more than one functional role that is set by interactions with other areas. With this in mind, it is possible that the portions of RPFC identified presently can be involved in retrieval mode and retrieval success, dependent on what other areas are functionally linked.

There is an important theoretical reason for focusing on systems-level interactions. If one considers that the nervous system is configured of interconnected elements, from local networks to large-scale ensembles, then it follows that much of what the brain does should be carried out through interregional interactions [Mesulam, 1990; McIntosh and Gonzalez-Lima, 1994]. Measures of regional activity alone may misrepresent the function performed by that region. A full appreciation of the functional significance of activity within a brain region can only be gained by examining it in the context of interactions with other parts of the brain.

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