Analysis of Intersubject Variability in Activation: An Application to the Incidental Episodic Retrieval during Recognition Test

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Abstract: Since the brain may engage different neuronal systems for a single behavioral goal, activation may show intersubject variability expressed in the systematic recruitment of multiple distinct networks. We apply a principal component analysis (PCA) to activation over task conditions and subjects to reveal cortical networks that may underlie this intersubject variability. Normal subjects were presented with novel meaningless objects, which appeared in personally familiar or unfamiliar places. During a subsequent, event-related functional MRI (fMRI) experiment, each subject was presented with learned or novel objects in isolation and performed a learned/novel judgment. Recollection of places was not essential for the task, and may exhibit large intersubject variations. The right posterodorsal posterior cingulate cortex (pPCC) and left retrosplenial cortex, whose involvement in place-recognition has been previously established, were selected as regions of interest for the PCA. Neural responses to objects associated with familiar relative to unfamiliar places in pPCC, but not in the retrosplenial cortex, were negatively correlated with task-related activation (common over all objects) in the right anterolateral prefrontal cortex and the left intraparietal sulcus. The latter areas have been implicated previously in cognitive control and object recognition, respectively. These results suggest right prefrontal control over neural processes both in the left parietal cortex, related to object-recognition (enhancement), and pPCC, related to nonessential recollection of place-memory (suppression), but not in the retrosplenial cortex, related to the sense of familiarity. This analysis revealed an important aspect of functional anatomy that was not detectable using a conventional analysis of average activations. *Hum Brain Mapp* 28:49–58, 2007. © 2006 Wiley-Liss, Inc.

Key words: memory; magnetic resonance imaging; echo-planar imaging; multivariate analysis; principal component analysis; prefrontal cortex; parietal lobe; gyrus cinguli

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INTRODUCTION

In the human brain, a single behavioral goal is often achieved using multiple neuronal mechanisms, some of which may be nonessential or incidental. This redundancy may confer behavioral advantages by affording cognitive operations that can be adapted to the situation or the individual. However, with respect to the functional imaging studies it may entail intersubject variability in cortical activation during cognitive tasks. This intersubject variability obviously reduces the sensitivity of conventional intersubject analyses [Friston et al., 1999; Holmes and Friston, 1998; Wei et al., 2004] because these between-subject effects are treated as noise. In a recent functional MRI (fMRI) study, Miller et al. [2002] reported a robust intersubject variability in activation during episodic retrieval, which speaks to a characterization of individual responses for full understanding of the cognitive mechanisms. In this article we look explicitly for systematic patterns of intersubject variability (which are orthogonal to the mean activations studied in conventional analyses) that may disclose important aspects of functional anatomy.

In this article we propose a novel approach to identification of brain networks, variably participating in the execution of a task, using a principal component analysis (PCA) of functional connectivity [Friston et al., 1993; Friston and Büchel, 2004; Horwitz, 1994]. The assumption is simply that a network for a specific cognitive mechanism will be activated differently in different subjects and that this will be expressed as a systematic pattern of intersubject variability. PCA was used to summarize patterns of variability, over subjects, in regions of interest (ROIs) showing task-specific effects. Inclusion of multiple ROIs and task conditions enabled us to extract patterns of intersubject variability in distributed networks induced by different conditions. The principal component scores entered a voxel-by-voxel multiple regression analysis of subject-specific activations (i.e., contrast images). The resulting statistical parametric maps identify cortical networks that participate in the principal modes of intersubject variability. The functional attribution of these principal components is based on the functional selectivity of the ROIs used in the PCA. This technique extends the application of PCA to PET data by Horwitz [1994] to focus on task-specific networks that are defined by ROIs with task-selective responses.

In the current study we applied our analysis to episodic recollection during recognition. Recognition is a good example of human cognitive mechanisms that can show redundancy; one usually recognizes a learned stimulus promptly, based on the sense of familiarity, but recollection of the learning episode can also occur, sometimes improving accuracy at the cost of speed [Yonelinas, 2002]. Incidental recollections, associated with recognized stimuli, are ubiquitous in daily life. Recent fMRI studies suggest that retrieval of sensory or action experience during recognition is associated with activation of cortical areas involved in sensory processing or action execution [Gottfried et al., 2004; Nyberg et al., 2000, 2001; Wheeler et al., 2000]. Conversely, in the context

of speeded recognition, incidental recollection of source memory may be suppressed, to deploy more cognitive resources to a goal-directed behavior. This can be conceptualized within the framework of the “supervisory system,” which can override routine behavior [Norman and Shallice, 1986]. Recent functional imaging studies addressing the neural correlates of successful suppression or inhibition [Anderson et al., 2004; Bunge et al., 2001; Hester et al., 2004; Rubia et al., 2003] have implicated the prefrontal cortex, often in the right hemisphere. This is consistent with neuropsychological observations of increased distractibility, by task-irrelevant stimuli and memories in patients with frontal damage [Chao and Knight, 1995; Shimamura et al., 1995; Woods and Knight, 1986]. Potential intersubject variability in the expression of these redundant recognition mechanisms may explain recent observations of large intersubject variability in cortical activation during episodic retrieval [Miller et al., 2002].

In this study, normal subjects learned objects presented in personally familiar or unfamiliar places. During a subsequent recognition task, where the objects were presented in isolation, neural activation was measured using fMRI. Recollection of the familiar place during object recognition is thus incidental to task execution, but potentially advantageous for accurate recognition [Yonelinas, 2002]. Given that retrieval of the learning experience during recognition is known to activate the cortical areas engaged during that experience [Gottfried et al., 2004; Nyberg et al., 2000, 2001; Wheeler et al., 2000], we assumed incidental recollection of personally familiar places during object recognition would involve areas activated in processing of familiar places. Critically, we did not expect activation related to incidental recollection of familiar places in a conventional intersubject analysis of our data. This is because some subjects may engage incidental processing and some may not. Therefore, ROIs were obtained from a separate study that explicitly addressed the cortical mechanisms for recognition of personally familiar places, performed as a companion experiment using the same set of subjects [Sugiura et al., 2005]. Intersubject variability in activation was then characterized using PCA over these regions in our study.

Given the previous study, the posterior cingulate cortex was considered to play a key role in representation of familiar places. Activation in these regions during recognition of objects associated with places was expected to show intersubject variability. An important component of that intersubject variation may be suppression of incidental place-recollection for speeded task-execution. This would be expressed as negative correlations between activations in the posterior cingulate ROIs and regions involved in cognitive control. We accordingly hypothesized that subjects who activated place-memory regions in the posterior cingulate cortex, during recognition of objects associated with familiar places only, would show less activation in executive control regions, including the right prefrontal cortex, irrespective of the task conditions. In addition, if recollection of place-memory and its suppression improved recognition accuracy

Figure 1.

Examples of the visual stimuli employed in the learning session (a) and the fMRI session (b).

and speed, respectively, this improvement may be reflected in correlations between respective principal component scores and behavioral data over subjects.

This analysis of intersubject variability is complementary to a conventional analysis. It is complementary in the sense that it characterizes orthogonal variance components (the average response over subjects in a conventional analysis and the orthogonal variation around that average in the current analysis).

SUBJECTS AND METHODS

The experiment comprised a learning session and an fMRI session, which followed a separate fMRI experiment addressing the cortical representation of personally familiar places [Sugiura et al., 2005]. The results of the first experiment were used to define the ROIs used in the study reported here.

Subjects

Twenty-five healthy, right-handed volunteers (20 men and 5 women, age 18–31 years) participated in the study. All subjects had normal vision and none had a history of neurological or psychiatric illness. Handedness was evaluated using the Edinburgh Handedness Inventory [Oldfield, 1971]. Written informed consent was obtained from each subject prior to participation in the study.

Learning Session

Each subject viewed 12 color movies, each presenting a different novel, purpose-made meaningless object with the camera moving around the object to show its 360° view (Fig. 1a). Each object measured between 20 and 100 cm in each dimension and was red, yellow, or blue. Six of the 12 objects appeared in places that were familiar to the subject, such as the subject's office, house, cafeteria, or train station. The remaining six objects appeared in unfamiliar places, semantically comparable to the familiar counterparts, such as an unfamiliar office, house, cafeteria, or train station, respectively. The movies were prepared without the subject.

Therefore, each subject saw the 12 novel meaningless objects for the first time during the learning session. Each movie lasted about 10 s and was presented three times to each subject. This learning session was performed while the subjects were lying in the MRI scanner. The movies were projected onto a semilucid screen in front of the headcoil of the MRI scanner, which was viewed via a mirror. Each subject was instructed to learn all the presented objects carefully so that he/she could remember them during a subsequent test session. The fact that the place could be familiar or unfamiliar was not mentioned. Objects appearing in familiar and unfamiliar places were counterbalanced across subjects.

fMRI Session

During fMRI, each subject was presented with pictures of 24 meaningless objects without a background (Fig. 1b), 12 had been learned in the learning session, and the remaining 12 were novel. Each subject was required to judge, as quickly as possible, whether he/she had seen the object during the preceding learning session and to respond by pressing one of two buttons: the right index finger for learned objects, and the right middle finger for novel objects. Each picture was presented for 0.5 s with a pseudorandom intertrial interval (3.1–28.3 s). Each object ($n = 24$) was presented five times from different views. The learned objects for the fMRI session were photographed separately from the learning session pictures; thus, no picture was presented in both sessions. One hundred twenty pictures in total were presented over the 906-s fMRI session. After the fMRI session was completed, each subject was debriefed to check whether he/she had recognized the familiar places during the learning session and asked whether there was any subjective difference in recognition during the fMRI session between objects appearing in familiar and unfamiliar places.

fMRI Measurement and Image Preprocessing

Thirty transaxial gradient-echo images (echo time = 66 ms, flip angle = 90°, slice thickness = 3.5 mm, slice gap = 0.35 mm, field of view (FOV) = 200 mm, matrix = 64

TABLE I. Candidate regions (as derived from Sugiura et al. [2005]) for regions of interest (ROIs) and their differential activation in LF – LU in the current experiment

Structure		Talairach coordinates:	
		x, y, z	t value
Posterodorsal posterior cingulate cortex (pPCC)	R	2, -52, 26	2.35
Middorsal posterior cingulate cortex (mPCC)	M	0, -32, 42	ns
Retrosplenial cortex	L	-2, -40, 26	1.91
	R	6, -44, 20	ns
Posterior precuneus	L	-4, -72, 36	ns
Intraparietal sulcus	L	-50, -42, 46	ns

Talairach coordinates of peak activation in the areas activated during recognition of personally familiar places [Sugiura et al., 2005] are given. The contrast LF – LU was tested at each peak voxel, and the t value is given for significant activation ($P < 0.05$, without correction for multiple comparisons). The peak voxel was then used as a ROI when activation was significant. R: right, L: left, M: midline, ns: not significant.

$\times 64$) covering the whole cerebrum were acquired at a repetition time of 3020 ms using an echo planar sequence and a Siemens Sonata 1.5 T (Erlangen, Germany) MR scanner. Excluding the six dummy scans for stabilization of the T1-saturation effect, 300 volumes were acquired for each subject. Additionally, an anatomical T1-weighted dataset (MP-RAGE) was acquired. The following preprocessing procedures were performed using Statistical Parametric Mapping (SPM99) software (Wellcome Department of Imaging Neuroscience, London, UK): adjustment of acquisition-timing across slices, correction for head motion, coregistration to the anatomical image, spatial normalization using the anatomical image and the Montreal Neurological Institute (MNI) template, and smoothing using a Gaussian kernel with a full-width half-maximum of 10 mm. SPM99, rather than SPM2, was used to ensure compatibility with the results of our previous study [Sugiura et al., 2005]. Data from 6 subjects (5 men and 1 woman) with excessive head motion (more than 3 mm) were excluded. Therefore, data from 19 subjects were analyzed.

Conventional Subtraction Analysis

Each recognition trial was assigned to one of the following three event categories: LF—the subject recognized the object as learned, and the object had appeared in a familiar place during the learning session; LU—the subject recognized the object as learned, but the object had appeared in an unfamiliar place during the learning session; and NV—the subject judged the object as novel. Categorization of trials as learned (LF or LU) or novel (NV) was based on the subject's response during the fMRI session. Categorization of each place into familiar or unfamiliar (i.e., LF or LU) was based on the subject's report obtained during the interview after the fMRI session.

First, a conventional two-level approach for event-related fMRI data was adopted. A voxel-by-voxel multiple regression analysis of the expected signal changes for the three event categories, constructed using the hemodynamic response function provided by SPM99, was applied to the

preprocessed images for each subject. Statistical inference on contrasts of parameter estimates was then performed with a second-level between-subject (random effects) model using one-sample t -tests. The analysis was conducted for the contrasts LF – LU and (LF + LU) – 2 NV. Activations depicted by these contrasts reflect recollection of familiar places associated with the learned object and successful recognition of learned objects, respectively. The latter contrast was masked inclusively by LF – NV and LU – NV to ensure that the activations observed were present in both simple effects. For these contrasts, the statistical threshold was set to $P < 0.001$ for height, corrected to $P < 0.05$ for multiple comparisons using the cluster size (using $P < 0.05$ for the masks).

Selection of ROIs

ROIs were specified in the regions which had shown differential activation during recognition of personally familiar places compared with unfamiliar places in the preceding companion experiment [Sugiura et al., 2005]. The candidate regions included the right posterodorsal posterior cingulate cortex (pPCC), the middorsal posterior cingulate cortex (mPCC) on the midsagittal plane, the retrosplenial cortex, bilaterally, the left posterior precuneus, and the left intraparietal sulcus (Table I). Regions showing significant activation in LF – LU ($P < 0.05$ without a correction for multiple comparisons) were selected as ROIs to ensure that the regions were related to recollection of place over the subjects at the most liberal criterion.

Principal Component Analysis

To characterize intersubject variability in place-memory-related responses, we performed a PCA of the responses of two place-memory selective regions. The three event categories in the two ROIs activated in LF – LU (see Results, Table I) constituted the multivariate response (three event categories $\times$ two ROIs = six variables) and the 19 subjects constituted the observations, resulting in a matrix of 19×6 .

PCA was performed using a singular value decomposition of the mean-corrected matrix [Friston and Büchel, 2004] in MatLab (MathWorks, Natick, MA). Only eigenvariates (principal components) with a contribution (normalized eigenvalue) greater than 16.7% were retained (the Kaiser Criterion). To identify the cortical networks predicted by each eigenvariate, its scores were entered into a voxel-by-voxel multiple regression model of the contrast images using SPM99 (i.e., a further physiologically informed second-level analysis). The cortical networks showing positive and negative correlations with each eigenvariate were identified by testing for significant regressions using a series of *t*-tests, rather than an *F*-test. We used *t*-tests because we were interested in signed correlation between regions both within and across contrasts. To find the cortical network that correlated with a specific eigenvariate, commonly over event categories, the multiple regression analysis was performed using the average contrast (LF + LU + NV)/3 (masked with each of LF, LU, and NV; all the contrasts against baseline) as dependent or response variable. To find the cortical network whose LF – LU activation correlated with a specific eigenvariate, the analysis was applied to the contrast LF – LU (masked with LF against baseline). The statistical threshold was $P < 0.001$ for height, corrected to $P < 0.05$ for multiple comparisons using the cluster size for each test (using $P < 0.05$ for height for the masks).

Correlation between Eigenvariates and Behavioral Data

To see whether there was an advantageous effect of place-memory on recognition accuracy (or speed), we tested the correlation between each eigenvariate and performance (percent correct response and the mean reaction times) over the event categories and the difference between LF and LU events.

RESULTS

Post-fMRI Debriefing

All but two subjects stated that they had remembered the familiar places during the LF trials only. The remaining two subjects stated that they were not sure whether they had remembered the familiar places.

Behavioral Data

The percent misses in the LF and LU events were $7.6\% \pm 8.7\%$ and $6.0\% \pm 5.4\%$, respectively, and the percent false alarms in the NV event was $3.2\% \pm 3.5\%$ (means $\pm$ standard deviations). The difference in the percent misses between the LF and LU events was not significant ($t(18) = 0.81$, $P = 0.81$). The mean reaction times in the LF, LU, and NV events were 934 ± 140 ms, 964 ± 149 ms, and 1069 ± 206 ms, respectively. The difference in the mean reaction times between the LF and LU events was not significant ($t(18) = 1.49$, $P = 0.15$).

Figure 2.

Significant LF – LU activation in two ROIs. Activated areas in the previous study [Sugiura et al., 2005] are projected onto the parasagittal plane of the mean normalized anatomical MRI [adapted from Sugiura et al., 2005] (top panels) and activation profiles (bottom panels) are shown for the right pPCC (2, –52, 26) (left panels) and left retrosplenial cortex (–2, –40, 26) (right panels). * $P < 0.05$, without correction for multiple comparisons.

Conventional Subtraction Analysis

When the whole brain was searched, no significant activation was observed in either the contrast LF – LU or (LF + LU) – 2 NV at the statistical threshold adopted.

Principal Component Analysis

Among six candidate regions (see Subjects and Methods), the right pPCC and the left retrosplenial cortex showed significant activation in LF – LU (Table I; Fig. 2). These were used as the ROIs for the PCA. The first, second, and third eigenvariates, with eigenvalues accounting for 38.5%, 22.2%, and 19.4% of the variance, respectively, entered into the connectivity regression model. The results of the voxel-by-voxel multiple regression analyses are shown in Tables II and III and Figure 3. The results for the contrast (LF + LU + NV)/3; the cortical networks in which the eigenvariates were correlated with the activations averaged across the event categories, are shown in Table II and Figure 3a. The first eigenvariate was positively correlated with activation in the posterior cingulate cortex including the pPCC and retrosplenial cortex, with peaks in the right and left hemisphere, respectively, the left precuneus, the left temporoparietal junction, the left middle temporal gyrus, the right anteromedial prefrontal cortex, and the left anterior cingulate cortex. No region showed a negative correlation with

TABLE II. Regions showing a correlation between the eigenvariates and mean activation over event categories

Structure	Talairach coordinates: <i>x, y, z</i>		<i>t</i> value	Cluster size (mm ³)	
First eigenvariate: positive					
Posterior cingulate cortex	L	-2, -40, 26	171.49	19,864	*
	R	2, -52, 26	47.07		*
Precuneus	L	-6, -60, 38	6.58		*
Temporoparietal junction	L	-56, -62, 24	5.54	2,728	
Middle temporal gyrus	L	-60, -6, -24	6.30	2,040	
Anteromedial prefrontal cortex	R	10, 56, -12	6.71	2,280	
Anterior cingulate cortex	L	-6, 48, 10	10.30	1,624	
Second eigenvariate: positive					
Posterior cingulate cortex	R	2, -52, 26	22.32	5,928	
Rostromedial prefrontal cortex	R	2, 34, -18	5.97	2,144	
Second eigenvariate: negative					
Intraparietal sulcus	L	-40, -44, 38	6.67	1,592	
Anterolateral prefrontal cortex	R	46, 48, 6	7.98	3,016	

Talairach coordinates of the peak and the respective *t* values, as well as the size of the cluster (mm³) of the regions where a significant correlation between activation, averaged over three event categories, and the eigenvariates was observed are shown; *t* values thresholded at $P < 0.001$, corrected for multiple comparisons by the cluster size ($P < 0.05$). L: left, R: right, M: midline.

* Indicates that the peak is involved in the same cluster.

the first eigenvariate. The second eigenvariate was positively correlated with activation in the pPCC and rostromedial prefrontal cortex, with their peaks in the right hemisphere, but negatively correlated with activation in the left intraparietal sulcus and the right anterolateral prefrontal cortex. No region showed any positive or negative correlation with the third eigenvariate.

The results for the contrast LF – LU, that is, the cortical networks in which the eigenvariates were correlated with LF – LU activation, are shown in Table III and Figure 3b. No region showed either a positive or a negative correlation with the first eigenvariate. The second eigenvariate was positively correlated with activation in the pPCC, with the peak in the midline. No region showed a negative correlation with the second eigenvariate. The third eigenvariate

was positively correlated with activation in a widespread posterior-medial cluster including the posterior cingulate cortex, cuneus, precuneus, and superior occipital sulcus, the left occipitotemporoparietal junction, and the medial prefrontal cortex with two peaks in its left anterior and right rostral parts. No region showed a negative correlation with the third eigenvariate.

Correlations between Eigenvariates and Behavioral Data

No significant correlation between eigenvariate and performance data (percent correct or mean reaction times) was observed; either in the mean over the event categories or the difference between LF and LU events.

TABLE III. Regions showing a correlation between the eigenvariate and LF – LU activation

Structure	Talairach coordinates: <i>x, y, z</i>		<i>t</i> value	Cluster size (mm ³)	
Second eigenvariate: positive					
Posterior cingulate cortex	M	0, -50, 24	14.61	4,032	
Third eigenvariate: positive					
Posterior cingulate cortex	M	0, -48, 26	27.08	23,752	*
Cuneus	R	2, -90, 16	5.89		*
Precuneus	L	-14, -78, 32	7.73		*
	R	12, -70, 30	6.93		*
Superior occipital gyrus	R	24, -80, 16	6.23		*
Occipitotemporoparietal junction	L	-44, -64, 38	6.57	1,344	
Anteromedial prefrontal cortex	L	-10, 58, 6	8.03	6,624	**
Rostromedial prefrontal cortex	R	8, 50, -6	5.50		**

The data are shown for the regions where a significant correlation between activation in LF – LU and the eigenvariates was observed.

* and ** indicate that the peaks are involved in the same cluster. Other details are the same as for Table II.

Figure 3.

Regions exhibiting a significant correlation between activation and eigenvariate. **a:** Results of the analysis performed on mean activation over three event categories. **b:** Results of the analysis performed on the LF – LU activation. The results of the analysis of the first, second, and third eigenvars are shown on the left, center, and right, respectively. Positive and negative correlations are presented in red and blue scales, respectively, on the “glass brain” of SPM99 (top panel: from the right, bottom panel: from the top).

DISCUSSION

Although no significant activation was observed in the conventional analysis of average activations, eigenvars (summarizing distributed patterns of activation) were significantly correlated, over subjects, with LF – LU activation in several cortical areas. These results are consistent with marked intersubject variability in the systematic activation of networks subserving incidental place-memory during object recognition. The second eigenvariate was positively correlated with LF – LU activation in the pPCC, and negatively correlated with mean activation over the event categories in the right anterolateral prefrontal cortex (Figs. 3, 4). These results are consistent with suppression of place-memory regions by the right prefrontal cortex.

A role of the pPCC in recognition of personally familiar places, arguably in allocentric spatial representation, has been postulated in our previous study [Sugiura et al., 2005], supported by its activation during autobiographical memory retrieval [Andreasen et al., 1995; Fink et al., 1996; Maguire and Mummery, 1999; Maguire and Frith, 2003; Mellet et

al., 2000; Piefke et al., 2003], but not during conventional experiments on episodic memory retrieval in which place-memory is not critical [reviewed in Sugiura et al., 2005]. Because the objects presented in the LF trials only were associated with familiar places, intersubject variability in this region appears to reflect that of place-memory recollection. The negative correlation in activation between the pPCC and the right anterolateral prefrontal cortex is consistent with the assumed role of the right prefrontal cortex in suppression of incidental memory-retrieval, based on neuropsychological [Chao and Knight, 1995; Shimamura et al., 1995; Woods and Knight, 1986] and functional imaging [Anderson et al., 2004; Bunge et al., 2001; Hester et al., 2004; Rubia et al., 2003] evidence. It is important to note that significant correlation between the right prefrontal activation and the second eigenvariate was observed commonly over the event categories, rather than LF trials only, which means that this suppressive mechanism prevents place-memory recollection, rather than recruitment as a response to the retrieved place-memory. A role of the left intraparietal sulcus in object recognition has been implicated in functional imaging studies of attention to a local feature of two-dimensional objects [Fink et al., 1997; Schubotz and von Cramon, 2001], and in the observation of manipulable objects [Chao and Martin, 2000; Grefkes et al., 2002; Handy et al., 2003; Sugiura et al., 2005]. Functional interaction between this region and the right anterolateral prefrontal cortex may suggest a role of the right anterolateral prefrontal cortex in enhancement of the left parietal object-recognition processes. A recent fMRI study has shown enhanced functional connectivity between the right anterolateral prefrontal cortex and the domain-specific posterior regions by increased task demands in each domain (verbal or spatial) [Sakai and Passingham, 2003]. The results of this study suggest that the right anterolateral prefrontal cortex both enhances and suppresses task-relevant and irrelevant processes, respectively, speaking to a pivotal role of this region in cognitive control.

The eigenvalue (contribution) of the second eigenvariate showed that the variance in activation pertaining to this right prefrontal control mechanism explains the second largest component (22.2%) of the total intersubject variance observed in the two ROIs. This large variance reasonably explains a lack of significant activation in the conventional subtraction analysis. The results highlight a limitation of the conventional subtraction approach under large intersubject variability, and a potential for our approach to identify brain networks underlying this variability. Although the existence of the intersubject variability in activation of a network related to the right prefrontal control is evident, its behavioral or cognitive contribution to the recognition test is unclear. The subjects with a lower score in the second eigenvariate (greater activation in the right prefrontal cortex) might have performed the task more promptly, or required more attention to maintain task performance. Those who had a higher score might have been less motivated or more proficient.

Figure 4.

Detailed results for the second eigenvariate. Top panels present the regions showing significant correlation, superimposed onto slices of the mean normalized anatomical MRI of all subjects. Bottom panels show plots of activation (parameter estimates) (y-axis) against the second eigenvariate (x-axis) in the three event categories for all subjects. A regression line is shown for each

event category in each region. **a:** Positive correlation with the LF – LU activation in pPCC. A left parasagittal slice ($x = -4$) is shown. **b:** Negative correlation with activations averaged over event categories, in the left intraparietal sulcus and right anterolateral prefrontal cortex. Coronal slices ($y = -44$ and 48) are shown.

Among the six candidate regions activated during recognition of personally familiar places in our preceding study [Sugiura et al., 2005], the pPCC and retrosplenial cortex only showed significant LF – LU activation, and were hence selected as ROIs. In addition to the pPCC, which possibly has a role in allocentric spatial representation [Sugiura et al., 2005], the retrosplenial cortex was differentially activated during recognition of an object associated with a familiar place. This is interesting given the suggested association of this region with the sense of familiarity [Shah et al., 2001]. The lack of significant activation in other candidate areas, such as the mPCC and left posterior precuneus, is consistent with our speculation in our preceding study that these regions do not directly support the representation of personally familiar places [Sugiura et al., 2005]. One should be aware that, in contrast to the allocentric spatial representation, which is irrelevant to the recognition test when speeded response was intended, the sense of familiarity is likely to play a role during recognition of all the objects when it concerns the 3D structure of the learned objects. It is then reasonable to assume that the suppressive effect, represented by the second eigenvariate, is exerted upon activation in pPCC only.

One might argue that the LF – LU activation may be related to the preparation of stimuli (i.e., the episode during

which the familiar places were photographed), rather than specific to the place-memory per se. We accept this possibility; in fact, no episode is free from a specific place, and any personally familiar place is associated with at least one episode. However, each subject did not witness the stimulus preparation, and recollection was incidental for the recognition task irrespective of its functional interpretation.

Although a decrease in activation of relevant cortical areas during active suppression has already been shown in a recent fMRI study [Gazzaley et al., 2005], we illustrate here a reciprocal activation pattern in the prefrontal cortex where the suppressive effect is likely to originate. We do not, however, argue direct causality of the right prefrontal suppressive effect on the pPCC, that is, a direct inhibitory projection, but do assume a simple causal relationship based on the neuropsychological evidence from patients with prefrontal damage [Chao and Knight, 1995; Shimamura et al., 1995; Woods and Knight, 1986]. Existing evidence suggests that the indirect effect is more plausible; an increase, rather than a decrease, in local field potential and regional blood flow was reported during direct stimulation of the inhibitory system in the cerebellar cortex of rats [Caesar et al., 2003].

The first and third eigenvariates were correlated with activity in overlapping cortical networks commonly over the event categories, and differentially in LF – LU, respectively.

The shared network composed of medial posterior and anterior cortices, as well as the left parietotemporal cortices. These areas are known to show task-induced deactivations [Gusnard and Raichle, 2001] and functionally be connected with each other during rest [Greicius et al., 2003], which is obviously a good explanation for the results of the first eigenvariate. These areas, however, also overlap with those activated during recognition of personally familiar places; the rostromedial prefrontal cortex was also activated in our previous study, although it was not reported since it did not survive correction for multiple comparisons [Sugiura et al., 2005]. This is reasonably followed by an interpretation that the third eigenvariate represents the residual variability in recollection of an object-associated place-memory, after variability in the right prefrontal modulation (the second eigenvariate) has been taken away. The overlap of the network of task-induced deactivation and that for place-memory retrieval is not surprising, considering that we are likely to be engaged in continuous or intermittent monitoring of an environment around us, a failure of which may cause disorientation. It is noteworthy that activation in a subset of this network is positively correlated with the second eigenvariate commonly over the event categories, suggesting that this network is also in part under the right prefrontal suppressive control.

Although we reported the results obtained with SPM99, for compatibility with our companion study [Sugiura et al., 2005], we also analyzed the data using SPM2 and obtained similar results. The results of the voxel-wise multiple regression analysis of the second eigenvariate include one outlier with a particularly small eigenscore. To exclude the possibility that the results were driven by this outlier, we repeated the analysis excluding this subject, and confirmed that the results did not change qualitatively.

CONCLUSION

Principal component analysis of intersubject variability revealed that the pPCC response, related to the place-memory recollection, was negatively correlated with task-related activation in the right anterolateral prefrontal cortex and the left intraparietal sulcus, whose roles in cognitive control and object recognition, respectively, have previously been suggested. The results illustrate intersubject variability in the right prefrontal control, including both enhancement and preventive-suppressive modulation, and thus is consistent with our assumption of intersubject variability in neuronal operation during recognition. Given the lack of significant activation in the conventional subtraction analysis, this ROI-based PCA of activation appears to be a useful supplementary approach to functional anatomy in the context of intersubject variability.

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