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Learning-Related Effects and Functional Neuroimaging

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Abstract: A fundamental problem in the study of learning is that learning-related changes may be confounded by nonspecific time effects. There are several strategies for handling this problem. This problem may be of greater significance in functional magnetic resonance imaging (fMRI) compared to positron emission tomography (PET). Using the general linear model, we describe, compare, and discuss two approaches for separating learning-related from nonspecific time effects. The first approach makes assumptions on the general behavior of nonspecific effects and explicitly models these effects, i.e., nonspecific time effects are incorporated as a linear or nonlinear confounding covariate in the statistical model. The second strategy makes no a priori assumption concerning the form of nonspecific time effects, but implicitly controls for nonspecific effects using an interaction approach, i.e., learning effects are assessed with an interaction contrast. The two approaches depend on specific assumptions and have specific limitations. With certain experimental designs, both approaches may be used and the results compared, lending particular support to effects that are independent of the method used. A third and perhaps better approach that sometimes may be practically unfeasible is to use a completely temporally balanced experimental design. The choice of approach may be of particular importance when learning-related effects are studied with fMRI. *Hum. Brain Mapping 7:234–243, 1999.* © 1999 Wiley-Liss, Inc.

Key words: memory; learning; medial temporal lobe; hippocampus; functional imaging; PET; fMRI

INTRODUCTION

In general learning systems, encoding of information, memory storage, and retrieval of stored information for flexible problem solving make it possible for learning systems to successfully adapt in a nonstationary environment [Arbib, 1995; Gabriel and Moore, 1990; McClelland et al., 1995; Vapnik, 1995]. From a parallel distributed processing perspective, learning in a neural network is a dynamic consequence of information processing and network plasticity [Amit, 1989; Arbib, 1995; Haykin, 1994; Hertz et al., 1991; Rumelhart and McClelland, 1986]. By hypothesis, this is also the case for the human brain [Petersson et al., 1997]. Learning and memory are fundamental brain functions, and characterizing the functional role of different brain regions involved in these processes is important for the understanding of the brain as a cognitive system [Fletcher et al., 1997; Nadel and Moscovitch,

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1997; Squire, 1992; Squire and Alvarez, 1995; Tulving and Markowitsch, 1997].

A fundamental problem when studying the effects of learning processes is that learning-related changes may be confounded by nonspecific effects, i.e., time effects not related to learning. This problem may be greater in functional magnetic resonance imaging (fMRI) studies compared to positron emission tomography (PET) studies of learning, given the problems with temporally correlated low-frequency noise, motion artifacts, and machine drifts using fMRI. There are several standard strategies for handling the problem with nonspecific time effects. Using the general linear model, one approach for separating learning-related effects from nonspecific time effects is to incorporate an explicit model of the nonspecific effects in the statistical model. Another strategy is to use an interaction approach, in which learning effects are assessed with an interaction contrast in the general linear model. A third strategy, that sometimes may be impractical, is to use a completely temporally balanced experimental design. Here we illustrate and compare the first two approaches by reanalyzing a PET data set of a previously reported learning study [Petersson et al., 1998]. The results relating to the medial temporal lobe (MTL) were reported in Petersson et al. [1997]. In brief, the results indicate that automaticity develops as a consequence of practice, and that this corresponds to a decreased dependence on attentional and working memory resources, as indicated by the practice-related decreases in the prefrontal, anterior cingulate, and posterior parietal regions. In addition, the results indicate that the activity of the MTL during retrieval decreases as a function of practice: in this case, repeated encoding and recall. This indicates an inverse relation between the strength of encoding and the activation of the MTL during retrieval [Mesulam, 1998]. Furthermore, the practice-related increases in the auditory and the posterior insular-opercular regions extending into the perisylvian supramarginal region may indicate a lesser degree of attentional suppression of task-irrelevant processing [Ghatan et al., 1998; Haxby et al., 1994; Jenkins et al., 1994; Schulman et al., 1997]. In addition, the practice-related increases in the right mid-occipitotemporal region may reflect aspects of more fully developed visual representations of the abstract designs processed during retrieval.

MATERIALS AND METHODS

The experimental paradigm and the procedures are described in detail in Petersson et al. [1997]. In brief, 12 right-handed, healthy male subjects (mean age, 24; range, 22–29) were included in the study (one subject was excluded in Petersson et al. [1997] because of asymmetric/partially missing data in the left MTL, and 6 + 2 scans were lost for technical reasons in 2 subjects, respectively). Each subject underwent 12 PET scans. The experimental paradigm consisted of two identical blocks (Fig. 1c). Within each block, scanning was done in three different states: the reference state (RS), novel recall (NR), and trained recall (TR). Each block consisted of six scans, with at least 10 min between scans in the order: RS1/NR/NR/training period/TR/TR/RS2.

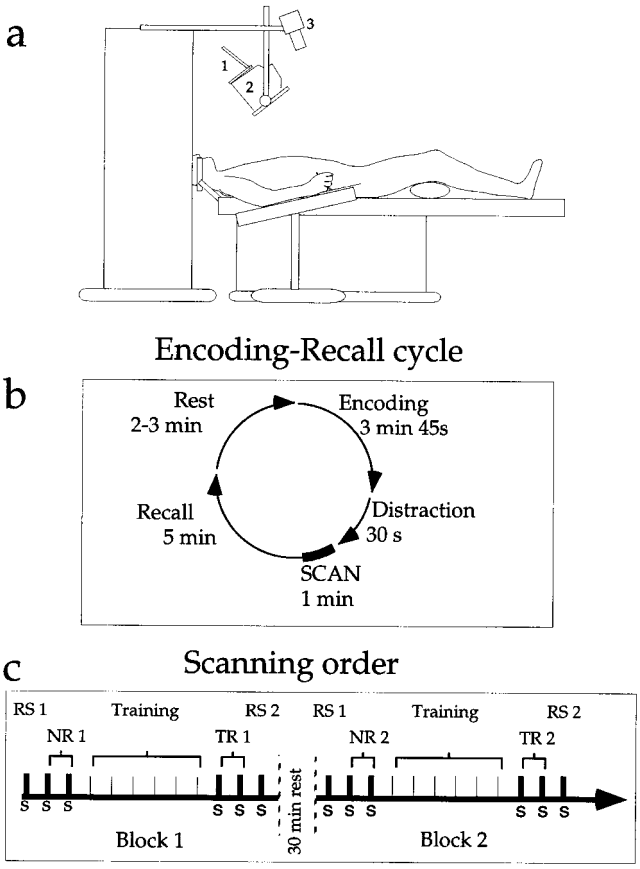

Figure 1.

a: Experimental PET scanner setup. 1, computer screen for presentation of the abstract designs to be copied during encoding; 2, monitor for closed-circuit visual feedback of the hand; 3, camera feeding into the monitor in the closed-circuit visual feedback. **b:** Encoding-recall cycle. During encoding, each of the 15 abstract designs was copied one time. Then a distracter text was read for 30 sec. Finally, during recall the designs were reproduced as faithfully as possible. **c:** Scanning order of the 12 scans: 2 reference state (RS), 2 novel recall (NR), and 2 trained recall (TR) scans in each block (bold markings; s, scanning), plus the training period (approximately 30 min) of 6 encoding-recall cycles in each block (thin markings).

In RS, the subjects filled in the contours of simple predrawn designs. Following the first RS scan in each block, the subject was engaged in the encoding-recall cycle (Fig. 1b). During encoding, a list of 15 separate abstract designs [Jones-Gotman, 1986] was shown for 15 sec each on a computer screen (Fig. 1a). In order to prevent recency effects, the subject read a nonsense text aloud for 30 sec after encoding [Baddeley, 1995]. After this, the retrieval was initiated and the PET scanning started. The subject reproduced the designs in any order. Two different lists of designs were used, one for each block, balanced over subjects. During each block there was a training period between the second NR scan and the first TR scan (Fig. 1c). The training period consisted of six encoding-recall cycles. Altogether, each subject went through 10 encoding-recall cycles and was scanned on the first two and last two recall procedures in each block.

Data analysis

The PET images were realigned, stereotactically normalized, and transformed into a common stereotactic space, as defined by the SPM95 template (an approximate Talairach space [Talairach and Tournoux, 1988]), 3D isotropic Gaussian-filtered (14 mm FWHM), proportionally scaled to account for global confounders, and analyzed with statistical parametric mapping (SPM95) [Friston et al., 1995]. To test hypotheses, estimates were compared using linear contrasts, and the resulting set of voxel values for each contrast was transformed into a Gaussianized t-field, i.e., a statistic image SPM[Z]. To reduce the false-positive voxels in activated clusters, the SPM[Z] was thresholded at 3.72 (or omnibus significance $P \leq 0.0001$).

Our experimental approach was based on the logic described by Raichle et al. [1994], i.e., introducing novel material of the same kind after the first learning block causes reactivation of the regions that showed practice-related effects in the first block. In order to model nonspecific monotone time effects as a linear confounding covariate, the PET paradigm of Raichle et al. [1994] was modified and extended to include two full repetitions of the basic experimental block.

The first approach for separating learning-related effects from nonspecific time effects explicitly incorporates a model of the nonspecific time effects in the statistical model, i.e., uses time as a linear or nonlinear confounding covariate in the general linear model. To the first order of approximation, it may be hypothesized that the nonspecific time effects are monotone and sufficiently well-approximated by a linear confound, or possibly nonlinear of low polynomial order. In the present report, we use the scan order and block repetition as confounding covariates in the general linear model.

The second strategy for handling nonspecific time effects uses an interaction approach, i.e., learning effects are assessed with an interaction contrast in the general linear model. This approach relies on the assumption that nonspecific effects are sufficiently similar in both the state of interest and the reference state. Specifically, the interaction approach relates data from a state of interest (in this case the recall state, i.e., NR and TR) to data from a reference state that is collected in temporal proximity under the assumption that both states are similarly influenced by nonspecific time effects. To do this, the RS scans acquired before the training period will be denoted RS1, and the RS scans acquired after the training period will be denoted RS2. Since all NR and RS1 scans were acquired before the training period and all TR and RS2 scans were acquired after the training period, we related the effects of interest in NR to RS1 and the effects of interest in TR to RS2. Specifically, we tested for learning-related effects using the contrast [NR-RS1] − [TR-RS2]. In contrast to the first approach, the interaction strategy implicitly controls for nonspecific effects, given that the underlying assumptions are sufficiently accurate. As a variation on the interaction theme, we also included block repetition as a confounding covariate.

The Karolinska computerized brain atlas (CBA) of Greitz et al. [1991] was used for the anatomical description of the activated regions described below. The SPM[Z], thresholded at $Z = 3.72$, was displayed in the CBA. The anatomical database of the CBA makes it possible to interactively determine the anatomical structures and Brodmann areas (BA) encompassed by an activated region. When a region is described to include a Brodmann area, this is not in an inclusive sense but only implies that parts of that BA are included. The resulting activated regions were characterized in terms of spatial extent and peak height of local maxima. As in Petersson et al. [1997, 1998], only regions of spatial extent that were significant ($P \leq 0.1$, corrected) are described. Likewise, only local maxima of significantly activated clusters are reported if the local maxima are significant ($P \leq 0.1$, corrected). All reported P values are corrected for multiple nonindependent comparisons based on the theory of 3D differentiable stationary Gaussian random fields [Adler, 1981; Friston et al., 1995; Worsley et al., 1992].

RESULTS

Comparing NR and TR using time as a linear confounding covariate

In what follows, we describe the significantly activated regions, including scan-order and block repetition, as confounding covariates in the general linear model.

Increases in novel recall compared to trained recall

The increases in NR compared to TR constitute a network of several activated regions (see Table Ia and Fig. 2a).

The prefrontal activations included the bilateral middle frontal/lateral orbitofrontal region (right $P = 0.03$, and left $P = 0.01$, BA 10, 11) and the left middle frontal region ($P = 0.004$, BA 9, 46, $P = 0.05$, BA 10). There were also left frontal opercular/anterior insular ($P = 0.06$, BA 45/49, 14) and small bilateral superior-middle frontal (right $P = 0.09$, left $P = 0.08$, BA 8 and left BA 6) activations.

The left anterior cingulate ($P = 0.006$) was activated in the left BA 24 and 32.

The parieto-occipital activations (right $P = 0.003$, left $P < 0.001$) included the bilateral superior parietal (left > right, BA 7) and the inferior parietal lobules (BA 19) extending into the superior parts of angular gyrus (left > right, BA 39).

The temporo-occipital and inferotemporal activations (right $P = 0.06$, left $P = 0.009$) included the left inferior occipital gyrus (BA 37), and the bilateral middle-inferior temporal gyrus (BA 37), extending into the left middle temporal BA 21.

The medial temporal and anterior occipitotemporal activations (right $P = 0.009$, left $P = 0.02$) included the bilateral BA 35 and 36, the right BA 34, the left BA 27, and the left BA 28.

Increases in trained recall compared to novel recall

In TR-NR, several significantly regions were activated (see Table Ib and Fig. 2c).

The opercular, mid-posterior insular, and supramarginal activations (right $P < 0.001$, left $P < 0.001$) included the bilateral perisylvian parts of supramarginal BA 40, the temporoparietal opercular region (BA 43, 50), the mid-posterior insular region (BA 13, 14), and the posterior opercular region (BA 44) extending into the superior temporal regions (BA 41/42/22).

The occipital activations included the right middle lingual region ($P = 0.02$, BA 19/37) and a small left posterior occipital region ($P = 0.08$, BA 18/19). In addition, a left pre/postcentral region ($P = 0.06$) was activated.

Comparing NR and TR using the interaction approach

Using the interaction approach, we included block repetition as a confounding covariate. The results were very similar when block repetition was not included.

Increases in novel recall compared to trained recall

In general, the results were similar to the results described above (Table II and Fig. 2). In brief, the prefrontal activations included the bilateral superior-middle frontal (right $P = 0.005$, left $P < 0.001$, and left $P = 0.05$, BA 10, 11, 46) and the left anterior cingulate (BA 24, 32) regions. The parieto-occipital activations (right $P = 0.02$, and left $P = 0.003$) included the left superior parietal (BA 7) and the bilateral inferior parietal (BA 39, 40, extending into right BA 19) lobules. The temporo-occipital activations (left $P = 0.10$, and $P = 0.08$) included the left middle-inferior temporal gyrus (BA 37, extending into BA 21). The medial temporal and anterior occipitotemporal activations (right $P = 0.03$) included the right BA 34 and the right hippocampus proper, as well as the left BA 28 and 36 ($P = 0.08$).

Increases in trained recall compared to novel recall

The opercular, mid-posterior insular, and supramarginal activations (Table IIb and Fig. 2d, right $P < 0.001$, left $P = 0.006$, and left $P = 0.008$) included the bilateral perisylvian parts of supramarginal BA 40, the temporoparietal opercular (BA 43, 50), the mid-posterior insular (BA 13, 14), and the posterior opercular (BA 44) region, extending into the superior temporal regions (BA 41/42/22). In addition, there was a right middle lingual activation ($P = 0.09$, BA 19/37).

Comparing NR and TR with RS focusing on the medial temporal lobe

In Petersson et al. [1997], one subject was excluded from analysis because of asymmetric or partially missing data in the left MTL. When this subject was excluded from the interaction analysis, the results in the MTL became more symmetric. More specifically,

TABLE I. Local maxima in the NR compared to TR when nonspecific time effects are explicitly modelled using scan order and block repetition as confounding covariates in the general linear model

a. Activations in NR compared to TR

Region	BA	x, y, z	Z-score	*P* value
Prefrontal cortex				
Superior / middle frontal g	6 dx	22, 4, 36	3.93	0.077
	6 sin	−26, −4, 44	3.94	0.075
	10 / 11 dx	22, 40, −12	4.55	0.008
	10 dx	24, 38, 0	3.96	0.071
	10 / 11 sin	−18, 44, −12	4.94	0.001
Middle frontal g	10 sin	−34, 52, 20	4.09	0.045
	9 / 45 sin	−44, 22, 28	4.54	0.008
	11 sin	−18, 28, −20	4.08	0.046
Anterior insula	14 sin[a]	−28, 24, 16	4.09	0.045
Frontal operculum / inferior frontal g	44 sin	−32, 6, 32	4.06	0.051
Anterior cingulate cortex	24 / 32 sin	−8, 20, 36	5.07	0.001
	24 / 32 sin	−14, 28, 20	4.31	0.020
Parieto-occipital cortex				
Superior / inferior parietal l	7 / 40 / 19 dx	40, −66, 44	4.21	0.029
	7 / 40 / 19 sin	−38, −66, 40	5.23	0.000
Inferior parietal l	39 / 19 dx	36, −72, 28	4.79	0.003
Angular g	39 sin	−36, −64, 36	5.23	0.000
Angular / middle temporal g	39 sin	−30, −48, 28	4.98	0.001
Medial temporal cortex				
Parahippocampal g	28 / 34 dx	20, −12, −28	5.26	0.000
	36 dx	30, −28, 20	4.85	0.002
Parahippocampal / fusiform g	36 sin	−34, −28, −20	5.15	0.001
Occipitotemporal / inferotemporal cortex				
Inferior temporal / fusiform g	37 dx	54, −48, −20	4.13	0.040
	19 / 37 sin	−54, −64, −16	4.33	0.018
Inferior temporal g	19 / 37 sin	−46, −76, −20	4.14	0.037

b. Activations in TR compared to NR

Posterior insula / operculum	13 / 16 / 50[a] dx	−38, −8, 12	5.82	0.000
	13 / 16 / 50[a] sin	−46, −4, 8	5.77	0.000
Superior parietal / postcentral	5 / 7 sin	−16, −38, 56	4.35	0.017
Superior temporal g	41 / 42 / 22 dx	48, −18, 4	6.88	0.000
	41 / 42 / 22 sin	−52, −26, 16	5.68	0.000
Occipital cortex				
Lingual g[a]	18 / 19 dx	10, −56, −12	4.56	0.007
Lingual g	18 sin	−12, −88, −4	3.83	0.106

BA, Brodmann area; g, gyrus; 1, lobule. [a] CBA. Coordinates refer to an approximate Talairach space. All *P* values are corrected for multiple non-independent comparisons.

comparing NR with TR using the interaction approach, there was a local maximum in the left parahippocampal / hippocampal region (BA 28 / 34, [x, y, z] = [−26, −10, −28], Z = 3.45), consistent with our previous ROI analysis [Petersson et al., 1997].

In order to compare NR and TR with RS / RS1 / RS2, and to compare the results with those reported in Petersson et al. [1997], we restricted the search volume to z-coordinates between +8 and −28 in Talairach space. We also excluded the MTL asymmetric subject

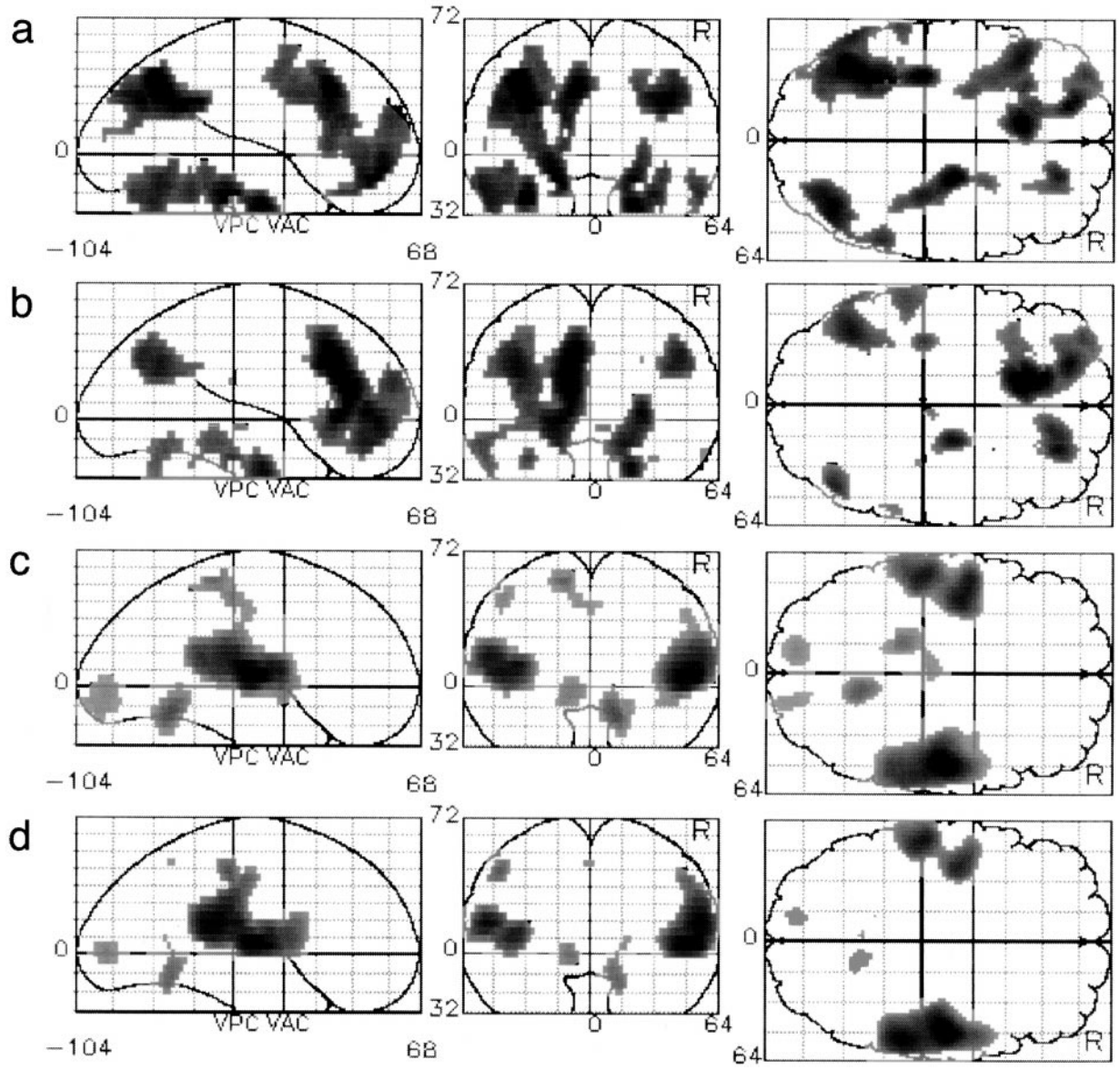

Figure 2.

Maximum intensity projections of activated regions. All images are thresholded at the omnibus significance level of $P = 0.0005$ ($Z = 3.29$). Activations in NR were compared to TR when (**a**) nonspecific time effects were explicitly modelled using scan order and block repetition as confounding covariates in the general linear model, and (**b**) using the interaction approach, i.e., nonspecific time effects were implicitly accounted for. Activations in TR were compared to NR when (**c**) nonspecific time effects were explicitly modelled, and (**d**) using the interaction approach.

and used a similar statistical model as in the interaction approach, with the order of scans within a given state as a confounding covariate (as in Petersson et al. [1997]; the results were similar if scan order was used as a confounding covariate or if no confounding covariate was used).

In NR compared to RS (=RS1 + RS2, see Fig. 3), there is a local maximum in the right parahippocampal gyrus (BA 28/35/36, [x, y, z] = [28, −24, −24], $Z = 4.56$, $P = 0.003$). The same local maximum MTL was also observed in NR − RS1 (BA 28/35/36, [x, y, z] = [28, −24, −24], $Z = 4.04$, $P = 0.055$). There were similar activations in the left MTL. The MTL was not activated in TR compared to RS or RS2. Thus, the results were similar to those reported in Petersson et al. [1997].

TABLE II. Local maxima when comparing NR with TR, using the interaction approach

Region	BA	x, y, z	Z-score	*P* value
a. Activations in NR compared to TR				
Superior / middle frontal g	10 / 46 dx	24, 40, 4	4.95	0.001
	10 / 11 dx	16, 40, −12	4.57	0.007
	10 sin	−22, 46, 0	4.81	0.002
	10 / 46 sin	−34, 52, 20	4.14	0.037
Anterior cingulate cortex	24 / 32 sin	−12, 20, 32	5.55	0.000
	24 / 32 sin	−14, 28, 20	5.53	0.000
	24 / 32 sin	−18, 24, 0	5.00	0.001
Parieto-occipital cortex				
Superior / inferior parietal l	7 / 40 sin	−38, −62, 28	3.96	0.068
Inferior parietal 1 / angular g	39 dx	44, −70, 32	4.58	0.007
	39 sin	−38, −62, 28	4.71	0.004
Medial temporal cortex				
Parahippocampal g	28 / 34 dx	20, −12, −28	4.93	0.001
	36 sin	−32, −26, −20	4.18	0.031
Occipitotemporal and inferotemporal cortex				
Fusiform g	37 sin	−56, −60, −16	3.97	0.064
Inferior temporal g	20 / 37 sin	−56, −36, −12	3.86	0.094
b. Activations in TR compared to NR				
Posterior insula / operculum	13 / 16 / 50[a] sin	−38, −10, 12	5.04	0.001
	13 / 16 / 50[a] sin	−46, −4, 8	5.77	0.000
Superior temporal g	41 / 42 / 22 dx	48, −16, 4	6.22	0.000
	22 dx	52, −36, 16	5.60	0.000
	41 / 42 / 22 sin	−52, −26, 16	5.33	0.000
Inferior parietal l	40 dx	46, −20, 40	3.97	0.065
	40 sin	−46, −30, 44	4.00	0.058
Lingual g[a]	18 / 19 dx	12, −58, −12	3.84	0.101

* BA, Brodmann area; g, gyrus; 1, lobule. Coordinates refer to an approximate Talairach space. All *P* values are corrected for multiple nonindependent comparisons.
[a] CBA.

DISCUSSION

A fundamental problem when studying learning processes is that learning-related changes may be confounded by nonspecific effects, i.e., time or repetition effects not related to learning. There are several standard strategies for handling this problem. In this report, we described and compared two such approaches. Another fundamental problem in the study of learning-related effects is the fact that learning or practice has effects on the performance of a task. This problem is not discussed in this paper (for a short discussion see Petersson et al. [1999]).

Our experimental approach was based on the logic described by Raichle et al. [1994], i.e., intro-

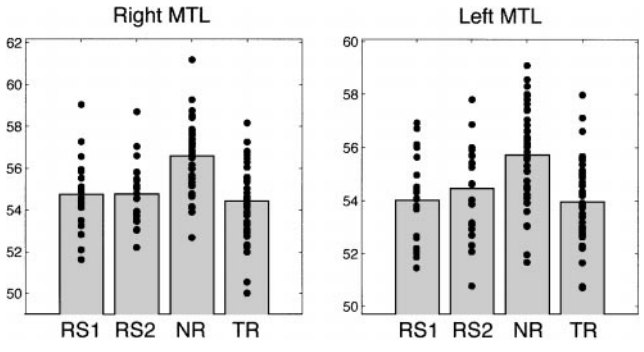

Figure 3.
Response patterns in the right and left MTL ([x, y, z] = [±28, −24, −24]), plotted as the adjusted rCBF over the different states (RS1, RS2, NR, TR).

ducing novel material of the same kind after the first learning block causes reactivation of the regions that showed practice-related effects in the first block. The PET paradigm of Raichle et al. [1994] was modified and extended to include two full repetitions of the basic experimental block. This allowed us to explicitly model nonspecific monotone time effects and block repetition as confounding covariates, using the general linear model. In addition, our experimental design allowed for an interaction approach.

The first strategy for separating learning-related from nonspecific effects uses time or scan order as a linear or nonlinear confounding covariate. This approach depends on the assumption or hypothesis of the general behavior of nonspecific time effects. Specifically, nonspecific effects have to be explicitly modelled. To the first order of approximation, it may be hypothesized that nonspecific time effects are monotone and sufficiently well-approximated by a linear confound, or are possibly nonlinear of low polynomial order. Since the major part of the results were similar and independent of the method used, this lends some support to this hypothesis. These results are also consistent with a recently reported analysis of task-independent effects of time on regional cerebral blood flow (rCBF) [Rajah et al., 1998], indicating that a major part of nonspecific time or repetition effects are monotone. However, linear covariates are most sensitive in picking up linear trends and cannot be expected to pick up nonlinear effects sufficiently different from linear trends if such effects are present. Hence, nonspecific time effects may not always be well-represented as linear trends.

The problem of nonspecific effects may be greater in functional neuroimaging studies using fMRI compared to PET, given the problems with temporally autocorrelated low-frequency noise (e.g., arising from different biorhythms), drifts relating to the physical performance of the MR scanner, and motion artifacts. Trying to account for nonspecific approximately linear trends may not be enough in studying learning-related changes with fMRI. In this context, the interaction approach may be a fruitful alternative strategy, i.e., data from a state of interest are related to data from a reference state that is collected in temporal proximity to the state of interest.

The interaction approach assesses learning-related effects with an interaction contrast in the general linear model. This approach implicitly controls for nonspecific effects by relating data from a state of interest to data from a reference state that is collected in temporal proximity to the state of interest. The interaction approach makes no a priori assumption on the form of nonspecific time effects. This implies that both nonlinear and linear nonspecific effects will be picked up. However, this approach relies on the assumption that nonspecific effects influence both states sufficiently equally. In general, this may not be the case, e.g., the task of interest may be very much less boring compared to a simple reference task. Another limitation with this approach is that learning effects of interest may be present in both the state of interest and the reference state and will thus not be detected, or only detected with reduced sensitivity.

Overall, the two approaches yielded similar results with three notable exceptions. Using the linear confound approach there were practice-related effects (NR-TR) in the frontal eye fields, the left anterior insula / frontal operculum, and the bilateral inferotemporal / occipitotemporal regions. Using the interaction approach, these regions, except for the left inferotemporal / occipitotemporal, did not show significant practice-related effects. This may reflect nonlinear, nonspecific time effects in these regions that are not sufficiently well-modelled with the linear confound approach. On the other hand, differentiating the reference state RS into RS1 and RS2 may reduce signal-to-noise, making this approach less sensitive. A third possibility is that the interaction approach controls for some aspects of procedural or other aspects of learning that are also reflected in the reference state in addition to nonspecific effects.

CONCLUSIONS

Since learning is correlated with time, particular care has to be taken so that learning-related effects are not confounded with nonspecific time effects. In the present paper, we illustrated and compared two different standard approaches to the analysis of learning-related effects. The two approaches described are based on the general linear model and depend on specific assumptions and have specific limitations. With certain experimental designs, both approaches can be used and the results compared, lending particular support to effects that are independent of the method used.

The first strategy explicitly models nonspecific time or repetition effects as confounds, and the second assesses learning-related effects with an interaction contrast, implicitly controlling for nonspecific effects. Overall, in the PET data analyzed here, the major part of the observed learning-related effects were independent of the method used. The results from the interaction approach constituted a major subset of the results from the linear confound approach. This may perhaps indicate that the interaction approach is less sensitive and more specific compared to the linear confound approach. However, alternative explanations are possible, and in general this may not be the case. This indicates that there is a need for both descriptive and inferential studies of learning-related as well as nonspecific time effects in functional neuroimaging data. Recently, a study of task-independent time effects was reported [Rajah et al., 1998], indicating that a major part of the nonspecific time or repetition effects are monotone, using a multivariate approach to the analysis of monotone time effects. The interaction approach, described here, makes no a priori assumption on the form of nonspecific time effects. This may be particularly valuable when learning-related effects are studied with fMRI. However, it should be emphasized that this approach is dependent on the assumption that nonspecific time effects influence both the state of interest and the reference state approximately equally, and that there are no learning effects of interest in the reference state. A third and better approach, when practically feasible, is to use a completely temporally balanced experimental design. The choice of strategy for handling the potential confounding of learning-related and nonspecific time effects may be of particular importance in fMRI studies.

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