

Task and Content Modulate Amygdala-Hippocampal Connectivity in Emotional Retrieval

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Summary

The ability to remember emotional events is crucial for adapting to biologically and socially significant situations. Little is known, however, about the nature of the neural interactions supporting the integration of mnemonic and emotional information. Using fMRI and dynamic models of effective connectivity, we examined regional neural activity and specific interactions between brain regions during a contextual memory retrieval task. We independently manipulated emotional context and relevance of retrieved emotional information to task demands. We show that retrieval of emotionally valenced contextual information is associated with enhanced connectivity from hippocampus to amygdala, structures crucially involved with encoding of emotional events. When retrieval of emotional information is relevant to current behavior, amygdala-hippocampal connectivity increases bidirectionally, under modulatory influences from orbitofrontal cortex, a region implicated in representation of affective value and behavioral guidance. Our findings demonstrate that both memory content and behavioral context impact upon large scale neuronal dynamics underlying emotional retrieval.

Introduction

Interactions between neural structures involved in memory and emotion are fundamental to reacting and adapting to biologically and socially significant stimuli, and thus to evolutionary viability. An emotional enhancement of learning is well established (Cahill et al., 1995; Dolcos et al., 2004; Richardson et al., 2004; Phelps, 2004), but mechanisms supporting retrieval of emotional memories have received little attention. A few recent neuroimaging studies have identified hippocampal and amygdala activity during emotional memory retrieval (Maratos et al., 2001; Phelps et al., 2001; Smith et al.,

2004b), raising the question of how these structures might interact, particularly because they are well interconnected anatomically (Amaral et al., 1992). A recent study by Greenberg and colleagues (2005) reported correlated activity in amygdala and hippocampus during autobiographical recall. Dolcos et al. (2005) compared neural activity during recollection of emotional and non-emotional photographs, and found that amygdala activity correlated better with medial temporal lobe (MTL) regions during emotional retrieval than during recall of neutral material. However, the nature and emotional valence of retrieval cues differed between conditions in that experiment, such that some experimental effects may be attributable to online processing of cue material (Maratos et al., 2001; Smith et al., 2004a, 2004b). Furthermore, even though this study suggested a functionally relevant increase of coupling between amygdala and hippocampus during emotional retrieval, no strong conclusions could be drawn. This was because the coupling analysis was based on correlating the local BOLD responses in amygdala and hippocampus across subjects. In contrast, we applied a causal model of effective connectivity to the neural activity of individual subjects, performing random effects analysis on the parameters. This allowed characterization of the reciprocal interactions between amygdala and hippocampus and how these connection strengths change as a function of stimulus material and task demands. Effective connectivity models examine how brain regions influence the activity of each other, without necessarily assuming the presence of direct connections between modeled regions. With dynamic models, this influence is determined by analyzing how the rate of change of activity (which relates to the “input”) of a region is influenced by the activity of connected regions.

The present experiment had two main aims: (1) to characterize dynamic interactions between brain areas implicated in emotion and memory in a way that excluded potential confounds because of differences in online processing of cue material and allowed for causal interpretations in terms of effective connectivity, and (2) to determine whether these interactions were modulated by the retrieval of emotional material per se or whether the interactions depended on the relevance of retrieved information to the current task. Importantly, we used a Bayesian model selection procedure (Penny et al., 2004) to compare several models of effective connectivity, each representing a different way in which amygdala-hippocampal interactions could be modulated by stimulus valence and task requirements, and then applied statistical tests to the optimal model.

To ensure that experimental effects could not be attributed to differences in online processing of retrieval cues, we used a contextual memory paradigm (Maratos et al., 2001; Smith et al., 2004a, 2004b) in which subjects encoded neutral objects in association with either neutral or negatively valenced photographic contexts drawn from the International Affective Pictorial System (IAPS) (Lang et al., 1997). At test, subjects then viewed neutral cue objects that had been associated with either neutral

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Table 1. Behavioral Performance Collapsed across Retrieval Tasks

Memory Context	Hit Rate	Source +	Source –	Source ?	Correct Rejection
Neutral	0.88 (0.08)	0.58 (0.11)	0.07 (0.05)	0.35 (0.08)	—
Negative	0.91 (0.07)	0.64 (0.09)	0.09 (0.04)	0.27 (0.06)	—
New item	—	—	0.18 (0.06)	0.82 (0.06)	0.89 (0.07)

Standard deviations in parentheses. Source +, proportion of recognized objects attributed to correct source. Source –, proportion of recognized objects attributed to incorrect source. Source ?, proportion of recognized objects in which source information was not remembered.

or emotional contexts during encoding or that had not been previously presented.

In order to examine whether neural interactions during retrieval of emotional memories were influenced by the relevance of retrieved emotional information to current task requirements, we employed two different source memory tasks. One of these tasks required subjects to judge whether a cue had previously been presented in association with a neutral or emotional context, whether it had previously been presented but contextual information could not be recollected, or whether it was a previously unseen cue. Note that this task required explicit processing of retrieved emotional information. The second task was similar but required source discrimination on the basis of recollecting whether or not people had been present in the context associated with the retrieval cue. Consequently, this task did not require explicit recollection and processing of emotional information from memory but made similar demands on memory retrieval to the emotional source task. Critically, this factorial design (comprising emotional valence and task as factors) allowed us to compare neural interactions during retrieval of emotional and neutral memories as a function of distinct task conditions while holding constant online perceptual aspects of the task.

Our initial hypothesis was that retrieval of information about emotional contexts would be associated with increased effective connectivity between hippocampus and amygdala, reflecting the outcome of emotional processing by the amygdala and engagement of a hippocampal episodic memory system. We also predicted that effective connectivity might be influenced by the “cognitive set” adopted by subjects during the task. It has been shown previously that neural activity during retrieval tasks can be modulated according to the type of material to be retrieved from memory (“retrieval orientation” effects) (Herron and Rugg, 2003; Hornberger et al., 2004). Different task requirements may engage various cognitive sets in order to optimize neural processing for the current task. We predicted that effective connectivity between amygdala and hippocampus would be enhanced when emotion was relevant to current task requirements, reflecting enhanced emotional processing of retrieved memory traces to support decision making.

Results

Behavioral performance was analyzed by ANOVAs of both recognition accuracy and source memory, incorporating factors of context valence, presence or absence of people in contexts, and retrieval task. There was no significant effect of retrieval task on performance ($F[1,15] = 1.87, p > 0.05$); therefore, subsequent

analyses were collapsed across task. Recognition accuracy and source memory performance, collapsed across retrieval task, are shown in Table 1. Items encoded in emotional contexts were more likely both to be recognized ($F[1,15] = 5.62; p < 0.05$) and to attract correct source judgments ($F[1,15] = 8.06; p < 0.05$) than items encoded in neutral contexts. This enhancement of memory for emotional stimuli is in accordance with previous findings (see Christianson, 1992). It is unlikely that the differences in source memory can be attributed to a response bias for emotional items given both the small proportion of recognized items receiving incorrect source judgments and that the small number of new items attributed a source judgment were no more likely to be attributed to emotional versus neutral contexts. Reaction times were not significantly different for items associated with emotional versus neutral contexts during either the encoding (6524 versus 6513 ms; $F(1,15) = 1.26; p > 0.05$) or retrieval (1975 versus 1964 ms; $F(1,15) = 1.57; p > 0.05$) tasks. This suggests that there were not significant differences in task difficulty when retrieving emotional or neutral information.

Within our neuroimaging data, we first identified differences in the neural activity that reflected retrieval of emotional compared to neutral information with an analysis based upon statistical parametric mapping (SPM) (Friston et al., 1995). We utilized a mixed event-related and epoch-based design within a single general linear model, allowing separation of item- and task-related effects (see Laurienti et al., 2003).

Item effects were determined by comparing event-related activity evoked by those retrieval cues and new items that elicited correct memory responses. At retrieval, items differed only in terms of their study history (old/new and encoding context) and therefore differences in neural activity could only be attributed to mnemonic processes, rather than differences between the items themselves (which could occur if intrinsically emotional material was presented at retrieval).

The pattern of activity common to retrieval of emotional and neutral source memories included areas previously reported in studies examining neural activity associated with recognition memory (Henson et al., 1999; Cansino et al., 2002), in particular left inferior parietal and bilateral prefrontal regions. Independent of task requirements, successful retrieval of source information from emotionally negative compared to emotionally neutral contexts (item effect) was associated with enhanced activity both in areas engaged by retrieval of emotional and neutral source memories and in distinct emotion-sensitive areas (Table 2A and Figure 1A), most notably left amygdala, a region previously reported in imaging studies of emotional memory retrieval (Maratos

Table 2. Brain Regions Identified in Emotional Retrieval Processing

	Region		Voxels	Peak Coordinates			Peak Z Score
				x	y	z	
A							
L	Lingual gyrus	(BA 19)	28	-18	-60	0	4.92
L	Cerebellum		28	-48	-51	-21	4.32
L	Supramarginal gyrus	(BA 40)	30	-60	-45	21	4.46
L	Pons		20	-9	-18	-24	4.39
L/R	Hypothalamus		14	-3	0	-6	4.41
R	Lateral globus pallidus		25	21	-6	-6	4.78
L	Amygdala		114	-24	-3	-18	5.42
R	Claustrium		25	27	15	-6	4.61
L	Inferior frontal gyrus	(BA 45)	7	-57	18	6	4.88
		(BA 47)	39	-33	30	-18	4.44
R	Inferior frontal gyrus	(BA 47)	26	36	27	-6	4.61
B							
L	Posterior cingulate	(BA 31)	11	-6	-66	24	4.15
R	Midbrain (SN)		49	12	-21	-9	5.01
L/R	Thalamus		61	3	-21	12	4.75
L	Hippocampus		15	-30	-21	-6	4.25
L	Anterior temporal lobe	(BA 36)	23	-27	-6	-33	4.08
L	Amygdala		42	-24	-6	-15	4.28
R	PHG/amygdala		54	36	-6	-15	5.19
L	Caudate body		20	-15	-6	24	4.69
L	Anterior Insula	(BA 13)	49	-39	15	3	4.65
R	Inferior frontal gyrus	(BA 47)	89	42	33	-9	5.17
L	Middle/inferior FG	(BA 11/45)	158	-42	36	-12	5.63
L/R	Med orbitofrontal cortex	(BA 11)	42	-3	48	-21	4.93

Significant effects were revealed by contrasts between (A) items attracting correct source judgments from negative versus neutral contexts, independent of retrieval task; (B) performance of emotion versus people contextual retrieval tasks.

et al., 2001; Phelps et al., 2001; Smith et al., 2004b, 2005). Item-related analyses of source hits versus misses and on the encoding data were performed (see [Supplemental Data](#)) showing similar patterns of activity to those previously reported (Smith et al., 2004b, 2005). These contrasts were not adopted for the subsequent connectivity analyses.

Comparison of neural activity associated with performance of the emotional versus nonemotional source task (task effects) was associated with increased activity in areas including bilateral amygdala, medial orbito-

frontal cortex, and left hippocampus (Table 2B and Figure 1B). Analysis of interactions between task- and item-related factors did not reveal any significant effects.

After we identified key regions engaged by emotional memory retrieval, our next goal was to characterize dynamic patterns of interaction between these regions as a function of either the valence of the contexts associated with studied test items (i.e., the emotional content of memories) or of the cognitive set under which the memories were processed (i.e., task requirement).

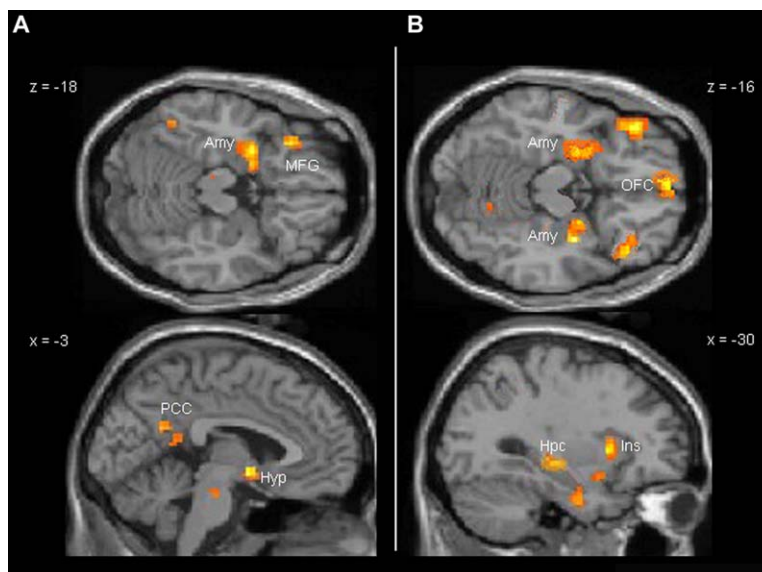


Figure 1. Effects of Memory Content and Task Requirements on Brain Activity

The figure shows the results from a random effects analysis across all 16 subjects ($p < 0.001$, uncorrected). (A) shows contrasts of recollection of items encoded in negative versus neutral contexts; (B) depicts contrasts of activity associated with emotional versus nonemotional retrieval tasks. Activity peaks are highlighted for amygdala (Amy), hippocampus (Hpc), orbitofrontal cortex (OFC), middle frontal gyrus (MFG), anterior insula (Ins), hypothalamus (Hyp), and posterior cingulate cortex (PCC).

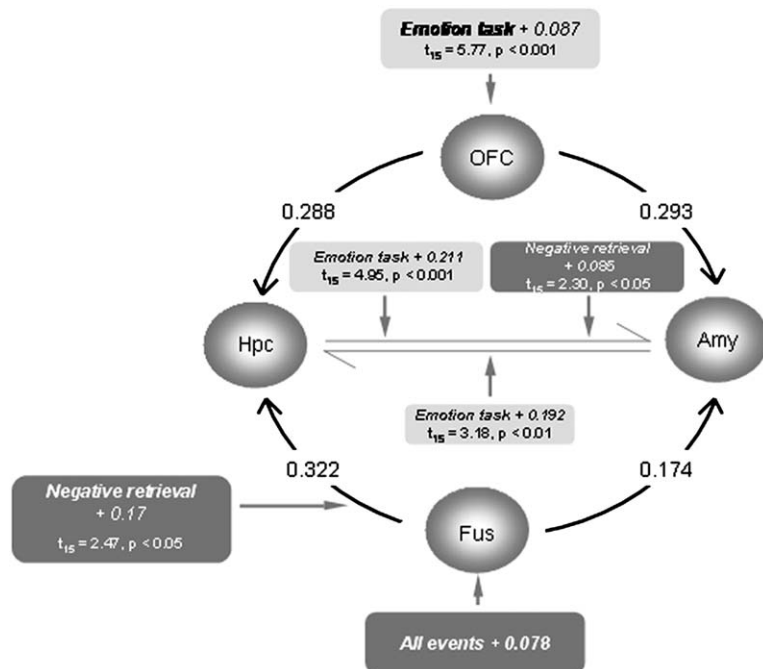


Figure 2. Dynamic Causal Model of the Neural Interactions in a Network Supporting Emotional Retrieval Processing

The model incorporated visual fusiform cortex (Fus), hippocampus (Hpc), amygdala (Amy), and orbitofrontal cortex (OFC). This model proved to be the optimal model out of seven different models tested (see main text). The values shown alongside connections represent (1) the group mean of the individual maximum a posteriori (MAP) parameter estimates of the modulation by the associated experimental factor, averaged across the 16 subjects, and (2) the result of the second-level analysis for that parameter estimate (paired t test across all 16 subjects). These modulations reflect the influence of memory content (retrieval of items from negative versus neutral contexts) (dark gray) and behavioral context (emotional versus people retrieval task) (light gray).

Consequently, we extracted subject-specific time series of local fMRI activity from left amygdala, hippocampus, and medial OFC. We also extracted time-series from a region of fusiform gyrus that showed responses to cue presentation across conditions in order to model visual input area for the network. As reliable activations in these regions could only be found in the left hemisphere of all subjects, we restricted our network model to the left hemisphere. The coordinates around which regional activity was extracted are given for each subject in the supplemental material. The responses in these regions were then used to estimate a series of seven dynamic causal models (DCMs) (Friston et al., 2003) per subject, each describing hypothetical mechanisms as to how variations in item valence and cognitive set modulated network dynamics. We then used a Bayesian model selection procedure (Penny et al., 2004) to determine that model that, across all subjects, provided the optimal balance between data fit and model complexity (see [Experimental Procedures](#)). This process determines the most parsimonious model, such that a less complex model will be favored over a more complex one that fits the data equally well. The subject-specific parameter estimates from this optimal model were then entered into two-sample t tests. This second-level group analysis tested for the intersubject consistency of how connection strengths were modulated as a function of (1) retrieval of information encoded in emotional versus neutral contexts, independent of task, and (2) task requirements to discriminate recognized items based on emotional versus nonemotional information.

Figure 2 illustrates the selected model (which was optimal in 15 of the 16 subjects tested) together with average effective connection strengths and significance of the effects of task and content factors on these connections. Subject-specific estimates of the effective connectivity parameters for all comparisons with significant results are presented in the [Supplemental Data](#).

Retrieval of information encoded in emotional contexts, as compared to retrieval from neutral contexts, increased connection strength from fusiform cortex to hippocampus ($t_{15} = 2.47, p < 0.05$) and from hippocampus to amygdala ($t_{15} = 2.30, p < 0.05$) (these effects were, however, only marginally significant after Bonferroni correction for multiple comparisons). Notably, these modulatory effects of item valence on connection strengths were task independent.

We next examined how the task requirements, in particular utilization of retrieved information to discriminate items according to emotional and neutral encoding contexts, influenced the pattern of interaction among selected regions. During the emotional, compared to the nonemotional, discrimination task, an enhanced pattern of effective connectivity was expressed bidirectionally from hippocampus to amygdala ($t_{15} = 4.95, p < 0.001$), and amygdala to hippocampus ($t_{15} = 3.18, p < 0.01$). In addition, during the emotional retrieval task, the strength of driving influences on OFC was increased ($t_{15} = 5.77, p < 0.001$), which in turn enhanced activity in amygdala and hippocampus. These effects of task on effective connectivity survived Bonferroni correction for multiple comparisons.

Discussion

Our findings reveal distinct patterns of brain activation associated with recollection of emotional and neutral contextual information, in line with previous findings (Dolan et al., 2000; Dolcos et al., 2005; Maratos et al., 2001; Smith et al., 2004b). Crucially, we also demonstrate that interactions between critical affective and mnemonic structures are modulated by cognitive set in a manner that reflects the task-relevance of emotional information. Processing differences in the retrieval of items associated with negative versus neutral contexts, independent of task requirements, are primarily

reflected in an increase in connection strength from hippocampus to amygdala, interactions between which are known to underlie encoding of emotional events (Cahill et al., 1995; Cahill and McGaugh, 1998; Phelps 2004). It has been established previously that the amygdala has a crucial role in indexing the occurrence of external emotional events (Hamann et al., 2002; Dolan, 2002), and amygdala activity has also been associated with emotional retrieval processes (Dolcos et al., 2005; Maratos et al., 2001; Phelps et al., 2001; Smith et al., 2004b, 2005). Our findings of increased effective connection strength between hippocampus and amygdala (Figure 2) suggest that these amygdala effects during retrieval reflect unique influences of emotional content during retrieval from episodic memory. The most probable explanation for our findings is that amygdala responds to and processes emotional information retrieved from hippocampus-dependent memory. Previous studies support an important role for the hippocampus during memory tasks dependent on retrieval of source information (e.g., Cansino et al., 2002; Dobbins et al., 2003), as in the present study. Furthermore, hippocampal-amygdala effects were predominantly in left hemisphere, consistent with previous studies of autobiographical memory (Maguire, 2001; Greenberg et al., 2005) as well as explicit processing (Gläscher and Adolphs, 2003) or retrieval (Smith et al., 2005) of emotional information.

It is possible that increases in effective connectivity reflect increased levels of recollection for valenced material, rather than a specific modulatory effect of emotion. Analysis was restricted to trials attracting correct source judgments, implying successful recollection of neutral and emotional contexts. The possibility that quantitatively greater amounts of information were recollected about emotional versus neutral contexts cannot be excluded, but previous studies have shown significant effects of emotional context at retrieval without modulating neural activity sensitive to recollection (Smith et al., 2004a).

The cognitive set engaged when behavioral responses depended on emotional discrimination judgments, and thus required explicit retrieval of encoding emotional context, was associated with increased effective connectivity between hippocampus and amygdala bidirectionally. We suggest that enhanced functional integration between these structures is likely to facilitate both memory retrieval per se and the emotional evaluation of the retrieved information. In this context, amygdala influences on hippocampus may serve either to promote hippocampally mediated recollection or to facilitate the re-encoding or reconsolidation of retrieved memories, a process shown to occur in rodent amygdala (e.g., Duvarci and Nader, 2004; Wang et al., 2005) and hippocampus (Debiec et al., 2002). The lack of significant interactions between task- and item-related effects supports the view that these effective connectivity changes reflected adoption of a particular cognitive set, rather than a context-related facilitation of item-specific activity, although strong interpretations cannot be drawn from the null result.

In addition to increasing effective connectivity between amygdala and hippocampus, the emotional discrimination task enhanced OFC activity, which in

turn increased activity in hippocampus and amygdala, constituting a top-down influence of cognitive set. This top-down influence from the OFC was paralleled by an increase in effective connection strengths between amygdala and hippocampus as described above. It may be that OFC modulates amygdala-hippocampal interactions, facilitating responses appropriate to the current cognitive set. Whether these contextual changes in effective connectivity are a direct result of OFC influences cannot be derived from our model. This would require modeling a direct modulation of the amygdala-hippocampal connections by OFC activity; this type of interaction would require second-order terms in the state equation (see Equation 1), which are not accommodated by the current implementation of DCM. Nevertheless, the engagement of the OFC in our paradigm is striking as it is a region associated with higher-order representation of affective value (Kringelbach and Rolls, 2004) and is critical in the emotional guidance of decision making (Bechara, 2004). The present findings suggest a similar role during retrieval of emotional information to guide current behavioral responses.

Our findings provide the first direct demonstration of the mechanisms that shape dynamic interactions, in specific task- and item-dependent fashions, between brain regions involved in mnemonic and affective processes during retrieval of emotional memory. We identify the dynamic nature of affective-mnemonic interactions during retrieval and show that the influence of higher cortical areas on these interactions is dependent upon behavioral context.

Experimental Procedures

List Construction

Photographs, drawn primarily from the IAPS (Lang et al., 1997) but supplemented from other sources, were used as encoding contexts. These contexts were factored according to whether they were negatively or neutrally valenced and whether or not they contained people. Selection of the contexts was based upon valence ratings by a separate group of twelve subjects (six female). 40 photographs were selected for each of four categories: neutral with people, neutral without people, negative with people, and negative without people, for a total of 160 encoding contexts. The slides containing people were balanced across valences in terms of the total number of people across all the contexts, the number of male and females, and the number of contexts depicting individuals, small groups, or large groups of people.

Eight study lists were formed by associating 320 neutral test objects with the selected contexts. These test objects were selected from object pictures across a wide range of semantic categories, which were rated by the same subjects as those who rated the contexts so as to exclude objects that were emotionally valenced or arousing. Each object was associated with a neutral context containing people in one list, neutral without people in a second, negative with people in a third, and a negative context not containing people in a fourth list. Objects were not paired with contexts bearing close semantic relationships to them. The contexts were ordered pseudorandomly, with the constraint that no more than three consecutive slides could be of the same valence or contain/not contain people. The objects were each then absent from four of the eight study lists and were available as new items for the corresponding test lists. Each study list had two associated test lists incorporating the 160 old items, 80 new items, and 60 "null events," allowing jittering of item onset times relative to task blocks. These were divided into 24 "blocks" of 10 events each during which subjects would perform either an emotional source judgment or a people source judgment. The different classes of test event (four types of old item, new items, and null events) were counterbalanced across the two

classes of task block. The order of task blocks was pseudorandom, with no more than two blocks of one task being presented consecutively.

Source Memory Task

16 (eight female) healthy right-handed volunteers viewed 160 pictures of neutral objects, each paired with a unique background photograph that served as an encoding context. These contexts were factored according to whether they were emotionally negative or neutral and whether they contained people or not. The pairing of objects and contexts was counterbalanced across subjects (additional details in [Supplemental Data](#)). Stimuli were presented to subjects via a mirror mounted on the head coil of the fMRI scanner, 50 cm from the projection screen. The horizontal visual angle subtended by the stimuli was approximately 3° for the contexts and 1° for the object pictures. Backgrounds were initially presented alone on the screen for 3 s, with the object picture then superimposed centrally for 5 s. Subjects were required to generate associations between background and object, responding with a key press when a meaningful association was attained. There was an interval of 1 s between trials.

After a further interval of 5 min, a source memory test, of which subjects were made aware before the encoding task, was administered. The 160 studied objects (but not the associated contexts) were intermixed with 80 unstudied (new) objects and presented in an identical manner to stimuli in the encoding task. Each stimulus was preceded by presentation of a white asterisk on a black background for 500 ms, followed by the retrieval cue for 1500 ms. A white fixation cross was then presented for 2200 ms before another asterisk signaled the start of the next trial. Two different source memory tasks were alternated during the test, with each task switch signaled for 10 s by written instructions as to which task to perform next. Each task block continued for 35 s, with the item onset times jittered within the block to allow separation of item- and task-related activity. In each task, subjects used a keypad to assign cues as belonging to one of four categories. For the emotion discrimination task these categories were new (item not seen during encoding), old and previously associated with a neutral context, old and previously associated with a negative context, or item is old but contextual details not recollected. The people discrimination task was similar except that old/neutral and old/negative categories were replaced with categories for old/with people and old/without people. Item-related effects were calculated by contrasting activity associated with old items attracting correct source judgments and correctly classified new items, during each of the source judgment tasks.

fMRI Processing

fMRI data were acquired from a 1.5T Siemens SONATA system (Siemens, Erlangen, Germany) equipped with a head coil. Functional magnetic resonance imaging (fMRI) was used to acquire volumes of 22 slices of 2 mm thickness (1.3 mm interslice gap), covering the entire brain except for the most dorsal aspects of frontal and parietal cortex and the inferior half of the cerebellum. We used a T2*-weighted echo planar imaging (EPI) sequence with a repetition time (TR) of 1.96 s, which had been adjusted to give optimal blood-oxygen-level-dependent (BOLD) contrast in the medial temporal lobe. Data were acquired during separate sessions for study and test, with the first five volumes of each session discarded to allow for T1 equilibration effects. Images were realigned and “unwarped” (corrected for interactions between movements and field inhomogeneities) ([Andersson et al., 2001](#)), normalized to a standard EPI template, resampled to a resolution of 3 × 3 × 3 mm, and smoothed with a three-dimensional Gaussian kernel with full-width half maximum (FWHM) of 8 mm.

Data were initially analyzed by a random-effects analysis in SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) ([Friston et al., 1995](#)). Regressors modeling stimulus events were convolved with a canonical hemodynamic response function. Linear contrasts of parameter estimates were estimated for each subject, and initial statistical parametric maps were generated. Task effects were modeled by convolving a box-car function with a canonical HRF. These event-related and task-related effects were modeled within a single mixed-design GLM, allowing separation of the influences of these factors on neural activity (see [Laurienti et al., 2003](#)).

Selection of Subject-Specific Regions of Interest

The regions of fusiform cortex, hippocampus, amygdala, and medial orbitofrontal cortex used for our dynamic causal model were defined within each individual subject on the basis of our initial random effects analyses. Data for our connectivity analysis was based upon computing the principal eigenvariate of the data across all significant voxels within a 4 mm sphere. The center of each sphere was located at the local maximum of the individual subject that was closest to the peak coordinates from the random effects analysis in the appropriate region. The closest maximum was chosen in each case so long as it was within 16 mm (i.e., twice the FWHM of the smoothing kernel) of the random effects peak and was identified as being within the appropriate brain region on each subject’s normalized structural scan. The coordinates of these areas in each subject are given in [Table 1](#). Because reliable activations in the regions of interest could only be found in the left hemisphere in all subjects, we defined our network model only for the left hemisphere.

Dynamic Causal Modeling

The connectivity parameters of our model were determined with Dynamic Causal Modeling (DCM), which is described elsewhere ([Friston et al., 2003](#)). In brief, DCM is a nonlinear system identification procedure, identifying the parameters of deterministic input-state-output dynamic systems with Bayesian estimation. Posterior density analysis determines the most likely coupling parameters given the data according to the observation model implied by the DCM and priors on the coupling and hemodynamic parameters.

Predictions about the observed data are based on a bilinear model of neural population dynamics that is combined with a hemodynamic model describing the transformation of neural activity into predicted BOLD responses. The neural dynamics are modeled by the following bilinear differential equation

$$\frac{dz}{dt} = Az + \sum_{j=1}^m u_j B^{(j)} z + Cu \quad (1)$$

in which z is the state vector (with one state variable per region), t is continuous time, and u_j is the j -th input to the modeled system (i.e., some experimentally controlled manipulation). This state equation represents the intrinsic strength of connections between the modeled regions (the A matrix), the modulation of these connections as a function of experimental manipulations (e.g., changes in task; the $B^{(1)} \dots B^{(m)}$ matrices) and the strengths of direct inputs to the modeled system (e.g., sensory stimuli; the C matrix). These parameters are derived from the time series with priors determined by neurophysiological factors and the model design and are scaled relative to a constant reflecting the intrinsic decay in neural activity in regions not receiving any extrinsic input. In a dynamic setting, units of connectivity are expressed per unit time, such that these parameters correspond to the rate constants of the modeled neurophysiological processes, with strong DCM connections reflecting influences that are expressed rapidly. As DCM estimates the influence of activity in one brain region on the rate of change of activity in another, rather than the activity level per se, the direction of influence can be more meaningfully determined than with static connectivity models.

Combining the neural and hemodynamic model into a joint forward model, DCM uses a Bayesian estimation scheme to determine the posterior density of the parameters. Under Gaussian assumptions, this density can be characterized in terms of its maximum a posteriori (MAP) estimate and its posterior covariance. These MAP estimates, whose values are assigned to the model parameters, can be analyzed by a second-level model to obtain statistical inference across a group of subjects (see below).

Overall, the parameters of the neural and hemodynamic model are fitted such that the modeled BOLD signals are as similar as possible to the observed BOLD responses. This allows one to understand and make statistical inferences about regional BOLD responses in terms of the connectivity at the underlying neural level.

Conventional analyses of fMRI data by linear convolution can be considered as a special case of the model described here. A DCM with intrinsic and modulatory connectivity between regions reduced to zero, and direct input to every modeled region produces a set of disconnected brain regions that respond only to extrinsic output.

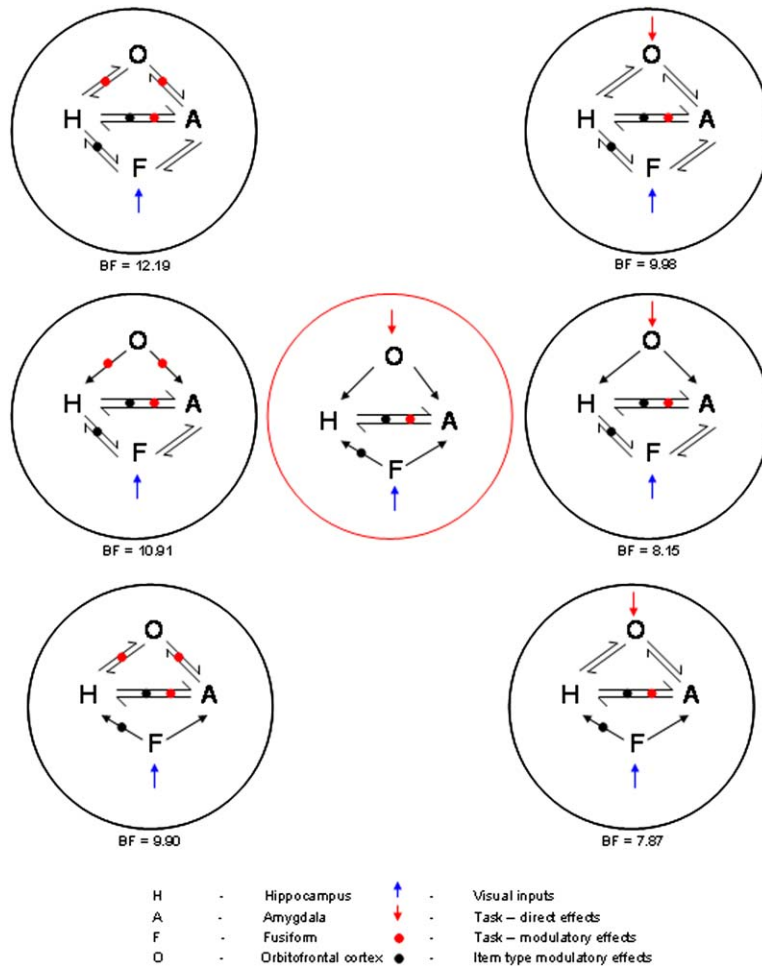


Figure 3. Diagrammatic Representation of the Seven Competing Models that Were Evaluated by Bayesian Model Selection

The optimal model is shown in the central red circle. For all other models, the average Bayes factor is given. This Bayes factor reflects the model evidence ratio of the optimal model and each alternative model, averaged across all 16 subjects (see main text). Comparing two models with identical evidence yields a Bayes factor of one. As shown by the figure, the Bayes factor was >7 in all cases, providing positive evidence for the optimality of the model selected.

Therefore the free parameters of interest are reduced to the input parameters (C), and by reducing the priors on self connectivity and hemodynamic parameters to zero, activity in each brain region can be determined with a convolution model as in most classical fMRI analysis (see Stephan, 2004).

Analysis of Connectivity Parameters

The models used for DCM described different hypothetical mechanisms as to how variations in item valence and cognitive set modulate the network dynamics. This characterization took account of two types of influence, involving either direct effects on regions (driving influences) or changes in their connection strengths (modulatory influences); see Figure 2 for details. A Bayesian model selection procedure (Penny et al., 2004) was used to determine which model represented an optimal balance between data fit and model complexity. The parameter estimates of the best model were entered into a second-level analysis. The question of interest, namely how connection strengths depended on item valence and cognitive set, was addressed in hypothesis-led paired t tests, together with Bonferroni correction for multiple comparisons, comparing the modulation by emotional items versus neutral items and by the emotional task versus the people task, respectively.

This group analysis tested for the intersubject consistency of how connection strengths were modulated as a function of (1) retrieval of information encoded in negative versus neutral contexts, independent of task, and (2) task requirements to discriminate recognized items based on emotional versus nonemotional information.

Alternative Models and Model Selection

For each subject studied, a large number of different models, incorporating different areas and connections, were constructed and fitted to the measured fMRI data. The models showing the best data fit

represented different hypotheses about how connection strengths between fusiform gyrus, amygdala, hippocampus, and orbitofrontal cortex depended on cognitive context. Representations of this subset of models are shown in Figure 3. For each subject, these models were formally compared by a Bayesian model selection procedure as described in Penny et al. (2004). In brief, given measured data y and two competing models m_1 and m_2 , this procedure computes the Bayes factor (BF), i.e., the ratio between the evidence of the two models:

$$BF(m_1, m_2) = \frac{p(y|m_1)}{p(y|m_2)} \quad (2)$$

Importantly, the model evidence does not merely depend on the accuracy (i.e., fit) of the model, but also on its complexity (i.e., number of free parameters). For a given subject, the optimal model, characterized by Bayes factors larger than one in comparison with all alternative models, thus represents an optimal balance between fit and complexity. As derived in Penny et al. (2004), a critical threshold for accepting one model to be better than another is to obtain a Bayes factor that is larger than Euler's number, i.e., $\exp(1) \approx 2.72$. An overall decision for a group of n subjects can be made by computing an average Bayes factor that corresponds to the n -th root of the product of the individual Bayes factors (note that multiplication is appropriate because model comparisons from different individuals are statistically independent). In the present study, the chosen model was optimal in 15 of 16 subjects. Quantitatively, across subjects, the average Bayes factor for comparing this model against the remaining six models ranged from 7.87 to 12.19, giving positive evidence that the selected model provided an optimal explanation, among all models tested, of the observed data across subjects (see Figure 3).

Supplemental Data

The Supplemental Data for this article can be found online at <http://www.neuron.org/cgi/content/full/49/4/631/DC1/>.

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