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ORIGINAL ARTICLE

Reduced Parahippocampal Connectivity Produces Schizophrenia-like Memory Deficits in Simulated Neural Circuits With Reduced Parahippocampal Connectivity

Lucia M. Talamini, PhD; Martijn Meeter, PhD; Brita Elvevåg, PhD; Jaap M. J. Murre, PhD; Terry E. Goldberg, PhD

Context: Episodic memory impairments are well characterized in schizophrenia, but their neural origin is unclear.

Objective: To determine whether the episodic memory impairments in schizophrenia may originate from reduced parahippocampal connectivity.

Design: Experimental *in silico* model.

Setting: Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands.

Interventions: A new, *in silico* medial temporal lobe model that simulates normal performance on a variety of episodic memory tasks was devised. The effects of reducing parahippocampal connectivity in the model (from perirhinal and parahippocampal cortex to entorhinal cortex and from entorhinal cortex to hippocampus) were evaluated and compared with findings in schizophrenic patients. Alternative *in silico* neuropathologies, increased noise and loss of hippocampal neurons, were also evaluated.

Results: In the model, parahippocampal processing subserves integration of different cortical inputs to the hippocampus and feature extraction during recall. Reduced connectivity in this area resulted in a pattern of deficits that closely mimicked the impairments in schizophrenia, including a mild recognition impairment and a more severe impairment in free recall. Furthermore, the schizophrenic model was not differentially sensitive to interference, also consistent with behavioral data. Notably, neither increased noise levels nor a reduction of hippocampal nodes in the model reproduced this characteristic memory profile.

Conclusions: Taken together, these findings highlight the importance of parahippocampal neuropathology in schizophrenia, demonstrating that reduced connectivity in this region may underlie episodic memory problems associated with the disorder.

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COGNITIVE IMPAIRMENT IN schizophrenia is broadly based, with varying degrees of deficit in different ability domains.[1-4] Particularly pronounced impairments are observed in episodic memory,[5,6] including moderate to severe deficits in free recall, lesser ones in cued recall, and a small but significant deficit in recognition.[5,7] These impairments do not appear to be related to an increased forgetting rate.[5-9] They are relatively unresponsive to medication,[5,10-12] age, and severity and duration of illness,[5] and can be identified in approximately 75% of patients.[13]

Until recently, the neural origin of the aforementioned deficits was unclear. However, recent in vivo imaging studies have related episodic memory performance in schizophrenic patients to volume[14,15] and activity measures in the (para)hippocampal region.[16,17] The pattern of neuropsychological impairment has also provided some indication of the brain regions involved. For instance, a frontal origin is improbable because the memory deficits are not correlated with attentive or executive aspects of memory processing.[4,5,18] Finally, the absence of amnesic signs argues against gross damage to the hippocampus proper (dentate and Ammon's horn).

The present study investigates whether medial temporal lobe (MTL) regions other than the hippocampus proper may underlie the observed deficits in schizophrenia, in particular, the parahippocampal

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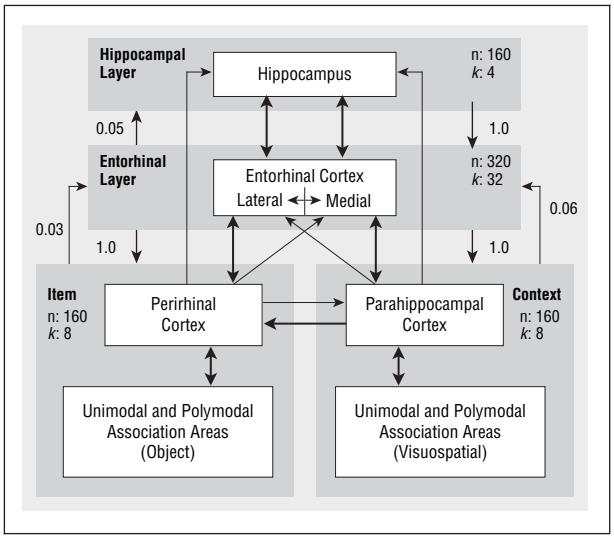

Figure 1. Simplified anatomy of the medial temporal lobe. The perirhinal cortex receives input from neocortical areas and a large "horizontal" projection from the parahippocampal cortex. Similarly, the lateral entorhinal cortex receives a feed-forward projection from the perirhinal region and a horizontal projection from the medial entorhinal cortex. The gray overlay depicts the 4 modules of the model. For each module, the number of nodes (n) and the global inhibition parameter (*k*) are shown. Model connections are depicted by arrows and a connection density (expressed as a proportion of 1).

region, including the entorhinal, perirhinal, and parahippocampal cortices. This region is adjacent to the hippocampus proper and forms the main source of its "sensory" input. Interestingly, this region shows the largest volume deficit within the MTL and substantial loss in the density of some synaptic and dendritic molecules.[19-21] Thus, it may be hypothesized that afferent, rather than intrinsic, hippocampal connectivity is preferentially affected in schizophrenia. According to current views of hippocampal functioning, this would leave the recurrent hippocampal pathways, subserving autoassociative storage and pattern completion, intact.[22] While our emphasis is on connectivity as a final common pathway for dysfunction, we are agnostic as to etiology. Reductions of connectivity may result from a variety of factors: environmental insult, failures in expression of trophic factors having to do with neurite growth, abnormal migration and attendant cytoarchitectural disruption, or factors in compromised neurotransmission that result in reduced functional connectivity.

It is difficult to envisage how parahippocampal abnormalities might affect memory processing, as their contribution is poorly understood. Therefore, an MTL memory model was developed that accounts for the differential role of this region in episodic memory. The model simulates performance in a number of typical episodic memory paradigms assessing recognition, retrieval, and interference. The consequences of reduced connectivity between parahippocampal regions and from these regions to the hippocampus in the model were assessed and compared with findings in schizophrenic patients. To evaluate the specificity of our findings, we contrasted the effects of reduced connectivity to other possible (although, in our view, less likely) abnormalities, such as "noise" and hippocampal neuronal loss. While the various symptoms of schizophrenia are likely related to multiple abnormalities at the neuronal level, the present results assist in understanding how a major cognitive impairment may result from a specific class of pathological changes, ruling in and ruling out candidate mechanisms.

METHODS

MODEL RATIONALE

An apparent function of MTL is to bind memories and their instance-specific context and then store these for later retrieval. The model described herein is based on studies showing that the bulk of hippocampal cortical input is segregated over 2 pathways.[23,24] One of these runs over the perirhinal area and targets the anterior and lateral entorhinal cortex; the other, via the parahippocampal cortex, projects mostly to medial posterior portions of entorhinal cortex. In primates, the perirhinal region conveys information regarding meaningful objects,[25,26] while the parahippocampal cortex is involved in memory for spaces and spatial relations.[27,28] These different aspects of an event may thus access the hippocampus over dual input streams.

The 2 streams are interconnected at various levels within the parahippocampal region[23,24] (**Figure 1**). These interconnections likely contribute to the integration of cortical inputs into a representation of their co-occurrence. In support of this notion, recordings of entorhinal neurons during delayed-response tasks indicate that their activity carries information about both objects and spatial locations.[29]

The hippocampus proper may quickly associate a small code to the conjunction of cortical inputs,[30-33] enhancing pattern separation in the system: similar entorhinal patterns are separated by their associated hippocampal patterns, which tend to resemble one another less than do the entorhinal patterns. Such de-correlation occurs through the combination of a dense projection from the entorhinal to the hippocampal layer, sparse firing in the hippocampal layer, and long-term depression in the connections from the entorhinal to the hippocampal layer.[34]

On the basis of the foregoing information, we implemented episodic memory storage as a process that entails 2 steps in binding: (1) First, item-context co-occurrence patterns are formed in the entorhinal cortex. We assume 1 such pattern is formed for each item-context combination. These relatively rich patterns are reciprocally connected with individual constituents (features) of the episode, which are themselves encoded in lower-order regions (perirhinal and parahippocampal cortices). The co-occurrence patterns show considerable overlap, because the context input may be similar for many item-context combinations (eg, in list-learning experiments). (2) In the second step, entorhinal patterns are reciprocally associated with small hippocampal codes with very little overlap. These hippocampal patterns are not directly associated with individual features, but serve to separate the large number of overlapping entorhinal patterns. The representational overlap in entorhinal cortex, combined with the pattern separation system in the hippocampus proper, enormously increases the storage capacity of the memory store with respect to any single layer system.[32]

We will show in following sections how this network organization sustains 3 interconnected functions that are crucial to episodic memory: (1) *sampling*, the process whereby a cue (part of previously stored information) is used to select a subset from multiple stored patterns in a memory store; (2) *pattern completion*, the activation of "missing" components of a representation through previously strengthened connections; and

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(3) *feature extraction*, whereby activated co-occurrence patterns lead to reinstatement of associated lower-order representations, which contain the feature information that the more abstract higher-order representations are lacking.

MODEL ARCHITECTURE

The model was built with the Walnut/Nutshell software developed by our group[35] and consists of linear threshold nodes. It captures the basic organization of the (para)hippocampal regions in a simplified manner, using 4 modules. All model connections are fanning (ie, contacted nodes are randomly distributed over the target layer), which is consistent with neuroanatomic data regarding most (para)hippocampal connections. None of the modules has intrinsic connectivity. The reciprocal connections between the hippocampal and entorhinal layers have a high learning parameter reflecting high plasticity. Conversely, plasticity of the connections from the 2 input layers to the entorhinal module is relatively low, so synaptic weights changed negligibly on the time scale of the simulations.

In both higher-level modules, global inhibition was mimicked by *k*-winner-take-all dynamics, which limits activity in a layer to a predetermined number of nodes (*k*) receiving the largest input. In accordance with electrophysiologic data,[29] *k* is relatively large in the entorhinal layer and small in the hippocampal layer. These and other parameter settings were obtained through optimization procedures for free recall. Parameter settings for the normal model are shown in Figure 1.

Learning was implemented with an asymptotic, hebbian-type rule,[36,37] in which the long-term expected value of weights is equal to the relative frequency of presynaptic and postsynaptic coactivation.[37] We used this characteristic to initialize most weights in our network to the value they would have after many independent patterns are learned (standard deviations were estimated with Monte Carlo simulations). This simulated the background of a "full memory." To also simulate earlier encounters of the subject with the items used in the list-learning experiments, we stored each item (including foils) in a random context, using a variable learning parameter. Retrieval was thus tested under competitive circumstances. These procedures were carried out for each permutation of the network, before running the actual simulations of memory paradigms. More methodologic detail is provided on the authors' Web site (http://www.neuromod.org/data/archives).

EPISODIC MEMORY PROCESSING

To simulate learning of an episode, a set of nodes is activated in the item layer and another set in the context layer. The patterns in the 2 input layers stimulate a set of nodes in the entorhinal layer. Out of this set, the nodes with the largest input become active, forming the entorhinal representation of the item-context co-occurrence. Some of the activated entorhinal nodes represent information from just one input layer, but most receive both types of input, and thus cross-associate the item and context patterns (**Figure 2**A). Similarly, the activated entorhinal nodes select a smaller group of hippocampal nodes. Through highly plastic, bidirectional connections between the entorhinal and hippocampal layers, these 2 representations are bound together, forming the episodic trace.

The memory system can be sampled by means of cues consisting of partial input patterns, for instance, part of a context representation from a previously experienced episode. Initially, such a cue may activate only part of an associated entorhinal pattern, but if the set of activated entorhinal nodes sufficiently resembles a stored representation, their combined firing will tend to activate associated hippocampal nodes, through the previously strengthened connections with these nodes. The hippocampal nodes, in turn, will recruit missing nodes of the entorhinal representation. Over a number of cycles, this pattern completion process will reinstate the original pattern in the entorhinal layer, which, in turn, can reinstate associated information in the input layers, namely, item representations that have been experienced in that particular context (feature extraction). Thus, all features of an episode can be recalled, even when only one of the input layers is cued.

SIMULATION OF EPISODIC MEMORY TASKS

General Procedures

Item and context representations consisted of sets of 8 nodes in the item and context layers, respectively. Item representations were nonoverlapping, while context representations overlapped randomly. During learning, synaptic transmission in the feedback connections of the hippocampal layer was dampened so that the activity in the network was largely determined by the "online" inputs.[38,39] Learning then occurred over 3 iterations for each item-context pairing. Following the learning session, synaptic transmission in the feedback connections was restored, to allow the influence of feedback activity during subsequent retrieval sessions.

As the performance measure, we used feedback from the entorhinal layer to the item representations. The assumption underlying this mechanism was that episodic memory only stores feature-impoverished co-occurrences of patterns that are themselves stored elsewhere, and that episodic retrieval serves to reactivate these patterns in the (cortical) brain areas where they are encoded. After cue setting, the model was allowed to update its activity over 50 cycles, or until any item representation reached threshold. If the feedback input to any item pattern (averaged over nodes that were within the pattern but not part of a cue) crossed a threshold, it was counted as retrieved, and the entorhinal and hippocampal layers were reset to a random activity state. Thresholds were set halfway between the distributions derived for feedback to the item layer for studied items and foils, respectively. Each simulation was repeated at least 50 times, with random initial settings; presented results are averages. Simulations were kept on a semiquantitative level (ie, parameter space was not searched to produce a best quantitative fit for the experimental data).

Procedure for Retrieval and Recognition

In typical episodic memory experiments, participants learn a list of items and then are asked to retrieve the learned material. List learning was implemented by presenting the model with a list of 10 items. The item representations were activated one at a time, together with one stable context representation, common to all the items. Here, "context" represents all information that remains stable over the course of the learning trial, such as the environment in which learning takes place. A characteristic of episodic memory is that retrieval is highly sensitive to context.[40,41] The model was allowed to learn each item-context combination. Retrieval was then tested under conditions representing free recall and recognition. In free recall, participants must reproduce the entire list, using only context information as a retrieval cue. A context cue was set by activating part (75%) of the context pattern that had been active during learning. In recognition, an additional item cue was given, consisting of 75% of an entire item pattern (not 100%, because aspects of item presentation may differ between study and test phase). This paradigm included presentation of foils

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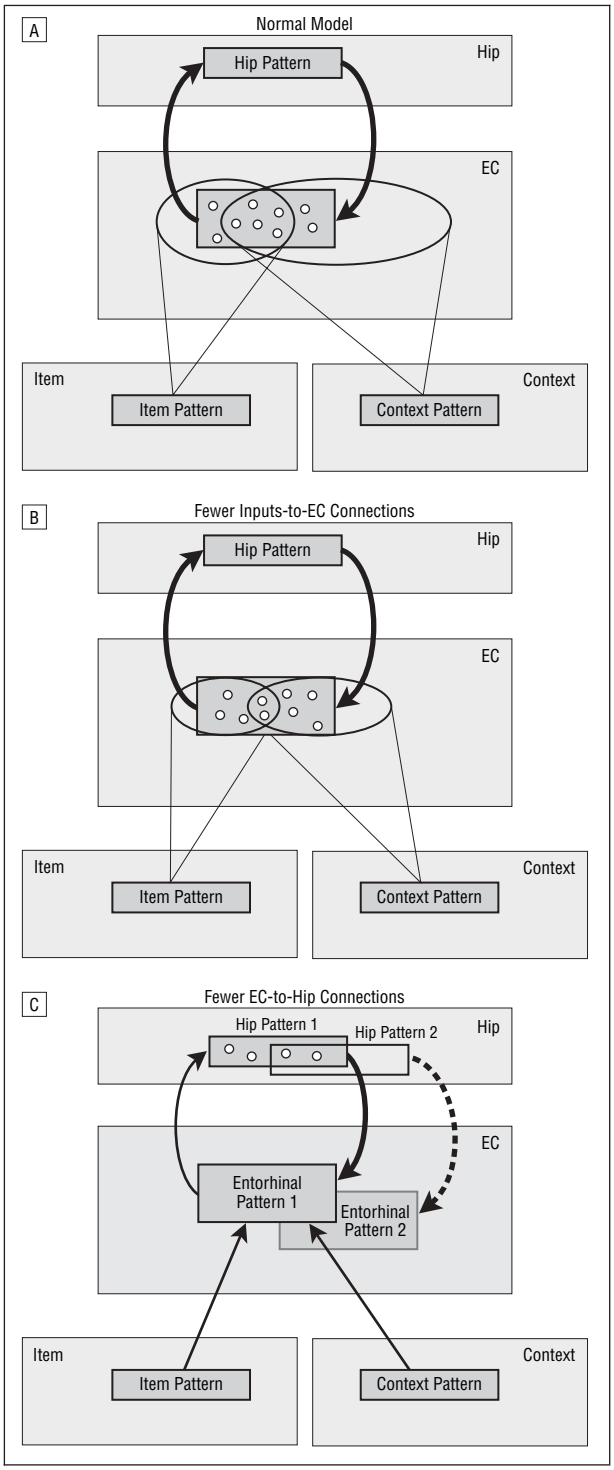

Figure 2. Formation of intersection patterns. At any time, the entorhinal pattern (represented by a box with nodes in the entorhinal layer [EC]) consists of the *k* nodes (where *k* indicates the global inhibition parameter) that receive the highest amount of input. A, In the normal model, most entorhinal nodes in a pattern receive inputs from both sources. As shown in the figure, these nodes reside in the intersection of the projections from the active item and active context pattern. They cross-associate lower-order item and context representations and are thus essential for successful free recall. B, Reduced input connections imply sparser projections from 2 concurrently active input patterns to the entorhinal layer and, thus, a smaller intersection of such projections. As a result, only a small part of the entorhinal pattern cross-associates the inputs. C, Reduced connections to the hippocampal layer (Hip) lead to a higher overlap between hippocampal patterns. Thus, any given entorhinal pattern will tend to activate parts of multiple hippocampal patterns. This decreases the likelihood of correct pattern completion through the hippocampal module.

Table. Basic Input and Retrieval Parameters for Simulated Paradigms

Paradigm	Input Nodes, No.		Nodes Cued at Retrieval, No.	
	Context	Item	Context	Item
Free	8 (Random overlap)	8 (Unique)	6	0
Cued	8	8	6	3
Recognition	8	8	6	6
AB-AC*	8 List 1	4/4 Pair A-B	6	4
	8 List 2	4/4 Pair A-C	6	4

Abbreviations: AB, the first list of cue words; AC, the second list of cue words.
*Fifty percent overlap in context between list 1 and list 2.

(items that did not occur on the studied list) at test, which had to be rejected.

In free recall, the number of different list items retrieved over 150 test iterations, with only the context cue set, was used as the performance measure. Intrusions were scored when an item not on the list was retrieved, omissions when list items were not retrieved. Any pattern reaching threshold during recognition was counted as an "old" response by the model, except when this occurred in response to a foil item; then a false alarm was scored. When no pattern was retrieved, a "new" response was counted. Parameters for each simulation are listed in the **Table**.

Procedure for Proactive Interference

Proactive interference was evaluated through a typical design, in which 2 lists of paired associates are learned sequentially. The task is to generate the second word of a pair (target word) when cued with the first word (cue word). Cue words used in the first list (the AB list) are repeated in the second list (the AC list), but are then associated with different target words (eg, *dog-lamp* in the first list, *dog-egg* in the second list). Participants are tested on the AB list after studying only that list, then they study the second list (AC) and are tested on it. A typical finding is decreased performance on the AC list with respect to the AB list, presumably because the first response associated with a cue word interferes with storage or retrieval of the second response associated with the cue.

The AB-AC paradigm was implemented with pairs of 4-node items. The simulation started with the successive presentation of 10 pairs in the AB list, which were activated with the associated context. The activations emerging in the model were learned. In a subsequent retrieval test, the model was presented with the first item of each item pair (cue word), as well as a 75% context cue. The model searched through memory for the associated target items. Next, the AC list of 10 pairs was learned with a second associated context and retrieval was tested again. To simulate that the 2 lists are presented during the same experimental session with only a brief delay interposed, the context patterns associated with the first and second lists overlapped by 50%.

In Silico Lesions

Schizophrenia was modeled as decreased connectivity from the input layers (item and context) to the entorhinal layer, and from the entorhinal to the hippocampal layer. Both sets of connections were decreased by 50%. Although the size of the reduction was chosen to clearly show the effects of the manipula-

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tion, reported reductions in synaptic markers in the hippocampal formation are indeed substantial. Harrison and Eastwood[21] reviewed connectivity-related alterations in the hippocampus proper: synaptic proteins were reduced by 25% to 60% and spine density by about 70%. Recently, spinophilin, a dendritic spine marker, was shown to be reduced in entorhinal cortex by 27%.[42] Connectivity findings are probably broadly similar in entorhinal and perirhinal cortices and the hippocampus (Paul Harrison, PhD, MD, e-mail communication, May 17, 2004). To analyze the effects of individual pathways, we also considered models in which just 1 of the 2 levels of connectivity (inputs-to-entorhinal or entorhinal-to-hippocampus) was reduced by 50%, as illustrated in Figure 2B and C.

To investigate the specificity of the schizophrenia manipulation, 2 alternative manipulations to reduced wiring were evaluated: progressively reducing nodes in the hippocampal layer, to test whether partial hippocampal damage could cause the deficits, and progressively increasing noise in the system's entorhinal and hippocampal layers. The latter manipulation was chosen in view of speculations that a decreased signal-to-noise ratio in regions involved in semantic processing may underlie some of the cognitive deficits in the disorder.[43] Both lesions are described in more detail in additional materials (http://www.neuromod.org/data/archives).

RESULTS

RETRIEVAL AND RECOGNITION

Normal Performance

The model was able to free recall, on average, 49% of list items in the given time. In recognition, the partly activated item representations guided the search process, leading to retrieval of 87.5% of patterns (**Figure 3**). The model produced only a small percentage of false alarms and intrusions. The relative performance of free recall and recognition is consistent with that in healthy subjects (Figure 3A and B).

Reduced Connectivity

The full (2-level) wiring manipulation resulted in a preferential reduction of free recall and a much milder deficit in recognition (Figure 3). The relative impairments in free recall and recognition accurately reproduce the data pattern in schizophrenic patients (Figure 3A and B). This is also the case when recognition is measured as d' (a signal detection measure of discriminability), with d' in the model and in schizophrenic subjects being reduced to 65.4% and 65.8% of control value, respectively.

The 2 levels of connectivity contributed differently to the memory impairment (Figure 3C): reduction of the lower level (inputs-to-entorhinal) severely impaired free recall, with only a slight reduction in recognition hit rate. In addition, false alarms were increased. These effects can be understood in the following manner: Successful free recall depends on the formation of entorhinal patterns in the intersection of projections from the context and the active item. However, the decreased density of input projections reduces the probability that a given entorhinal node receives input from both

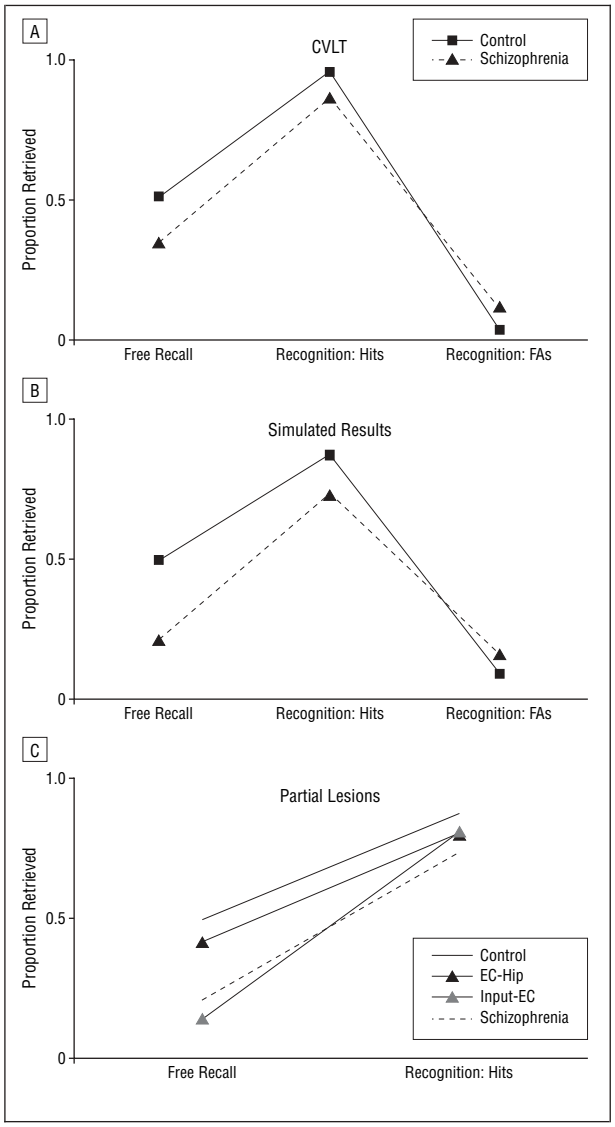

Figure 3. Comparison of real (A) and simulated (B and C) data showing the proportion of retrieved items in recall, the proportion of hits in recognition, and the proportion of false alarms (FAs) in recognition (ie, falsely recognized foils). Data from schizophrenic patients and healthy controls (A) were derived with the California Verbal Learning Test (CVLT), after the first learning trial (T.E.G., unpublished data, 2003). Model performance is shown after reduced wiring (B) and after separate reduction (C) of inputs-to-entorhinal (EC) or EC-to-hippocampal (Hip) connections. Maximal standard error of the mean in the graphs is 0.015 (with binomial distribution, 100 repetitions, and 10 learned patterns).

sources (see again Figure 2B). This favors the inclusion of nodes receiving only context or only item input in entorhinal representations. The latter nodes cannot be activated by the context cue, compromising free recall. Impairment is far less pronounced when item cues are additionally provided, because, with cues from both sources, entorhinal nodes receiving single-source input can potentially be activated.

In contrast, reduction of entorhinal outputs to the hippocampal module led to mild deficits on both memory paradigms. Here, the cause is hampered orthogonalization over the entorhinal-hippocampal pathway, increasing mean overlap between hippocampal patterns (from 6% to 13%). Consequently, nodes in the hippocampal layer activated over-

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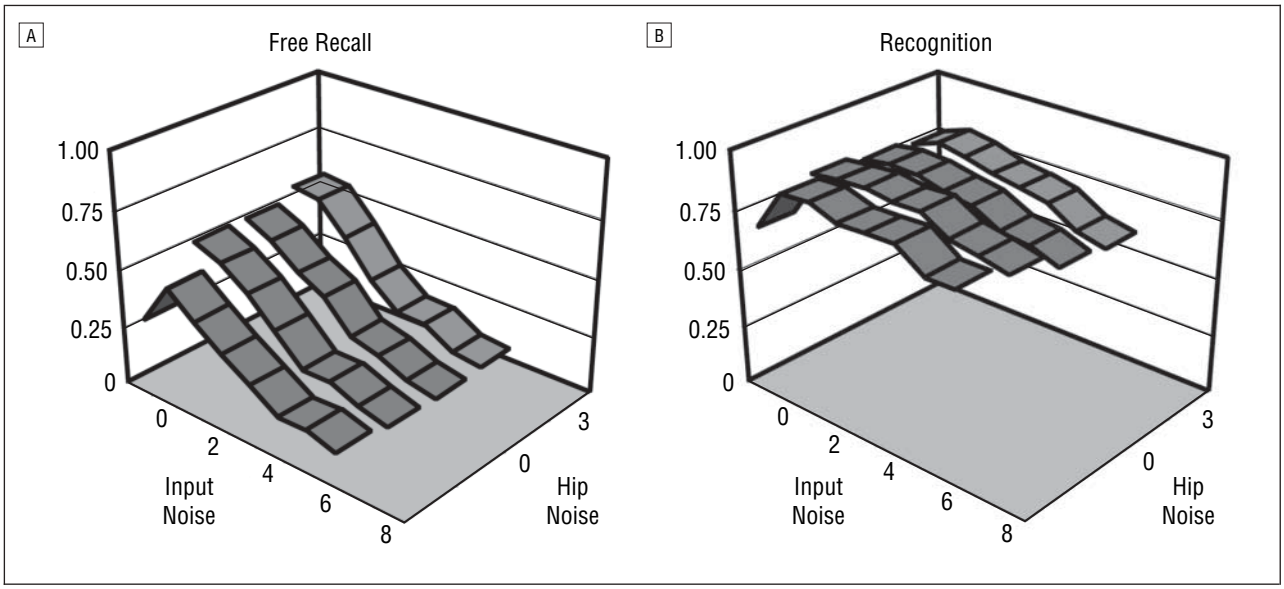

Figure 4. Influence on memory of noise in the input to the entorhinal layer (input noise) and in the input to the hippocampal layer (hip noise). Input noise was implemented by activating a number of random context nodes; hip noise, by simulating the inputs that a number of randomly activated entorhinal nodes would send to the hippocampal layer. A, Free recall. B, Recognition. y-Axis represents proportion of items retrieved.

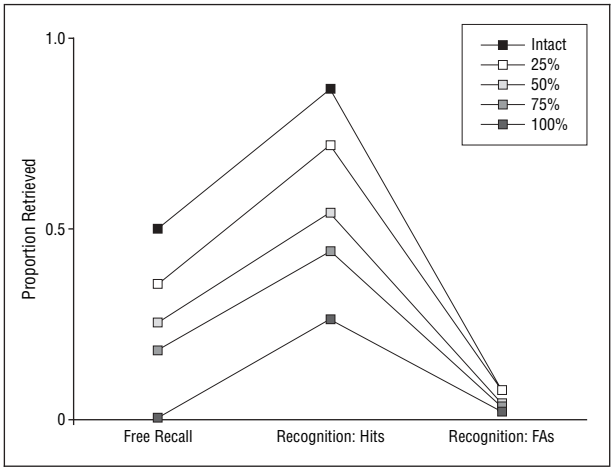

Figure 5. Influence of hippocampal node reductions on episodic memory. The size of the hippocampal layer is reduced in steps of 25% of the original size. FAs indicates false alarms.

lapping and competing representations in the entorhinal layer, resulting in fewer entorhinal patterns being completed by their hippocampal layer companion and fewer items reaching threshold (see again Figure 2C). Notably, this deficit involves not the sampling of memories, but their completion once they are sampled. Retrieval therefore suffers irrespective of cueing condition, and performance in both memory tasks drops to a similar extent.

In essence, the reduction of the lower level of connectivity caused episodic traces to be poorly associated to both cortical input sources. This preferentially affected retrieval after single-source cues, as in free recall. The reduction of entorhinal outputs to the hippocampal layer led to a mild deficit in pattern segregation, making some patterns entirely irretrievable. The schizophrenia memory profile resulted from the concatenation of these 2 problems.

Alternative Lesions

Both increased levels of noise (**Figure 4**) and lesions to the hippocampal layer (**Figure 5**) affected memory performance. Specifically, free-recall performance benefited from hippocampal noise but was highly sensitive to entorhinal noise. Recognition, on the other hand, was resistant to noise: although the maximal noise levels in the simulation provided more input than each cue separately, context and item cues were still able to guide retrieval to the appropriate patterns. At levels of noise where recognition performance did start to deteriorate, free recall had already reached extremely low levels.

For all grades of hippocampal node reduction, free recall, cued recall, and recognition were affected to a similar extent, while there were no increases in intrusions, false alarms, or responses in a novel context. In view of the global effects on memory performance, this pattern is akin to that seen after mild damage to the hippocampus proper,[44,45] rather than that described in schizophrenia. There was thus no degree of noise or of hippocampal node reduction that reproduced the episodic memory profile observed in schizophrenia.

PROACTIVE INTERFERENCE

In normal subjects, retrieval of items suffers from the presence of similar items in memory. These proactive interference effects appear to be dwarfed by the general memory deficit in schizophrenic patients (**Figure 6**A).[46,47] As an additional test of the model, we investigated whether it would reproduce these surprising findings.

Reduced Connectivity

In this simulation, both the control and the schizophrenia condition produced an interference effect, in that the

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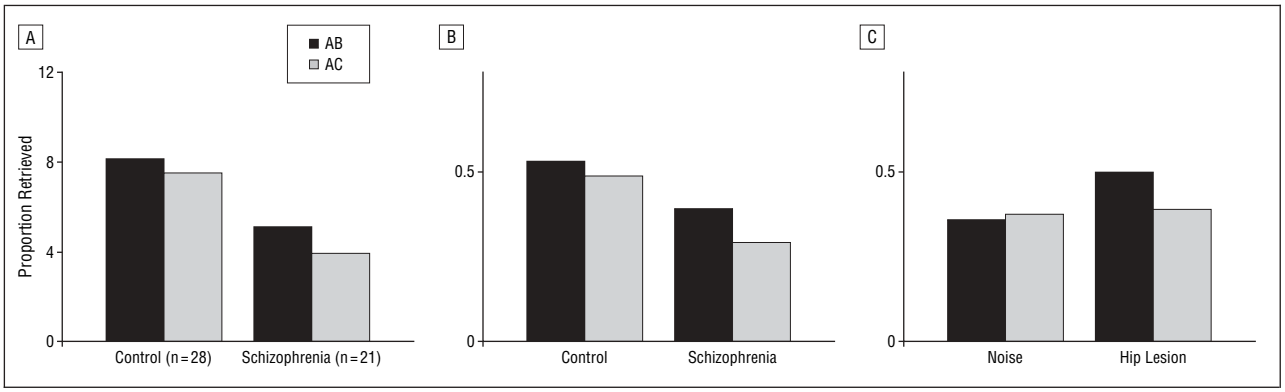

Figure 6. Comparison of real and simulated data on proactive interference. Retrieval rates for the first list (AB) and second list (AC) are shown for schizophrenic and healthy subjects from experiment 1 in the study by Elvevåg et al[46] (A) and corresponding simulated groups (B). C, Performance with the 2 alternative lesions is shown for maximal noise levels (8 additionally active entorhinal layer nodes and 3 additionally active hippocampal nodes), and for a 50% reduction in hippocampal nodes.

number of hits was lower on the AC list than on the AB list (Figure 6B). In raw scores, the interference effect was slightly larger in the schizophrenia condition (5% vs 10%). This was also the case in the study by Elvevåg et al,[46] but the observed difference was not statistically significant. We therefore subjected our data to a repeated-measures analysis of variance with model permutation (simulated schizophrenia, normal model) as the between-group factor and list (list 1, list 2) as the within-group factor. Not surprisingly, there was a main effect of group, due to the simulated patients' inferior performance ($F_{1,198}=1595.6$; $P<.001$), and of list, with performance on list 1 being superior to that on list 2 ($F_{1,198}=13.8$; $P<.001$). However, there was no significant interaction between group and list ($F_{1,198}=3.05$; $P=.08$), despite 100 simulated participants per model condition. As in Elvevåg and coworkers' analysis,[46] the interference effect was dominated by the overall memory deficit in the patient group.

As an additional measure of interference, intrusions were scored whenever the model produced a response associated with the first list (AB) during testing of the second list (AC). In line with Elvevåg and coworkers' results,[46] we did not find a preferential increase in the number of intrusions (from 10% of all answers in the intact model to 14% in the schizophrenia manipulation, which amounts to 20.3% and 20.7%, respectively, of all errors).

Alternative Lesions

As in the earlier simulations, the schizophrenia data pattern was not replicated with the use of alternative lesions (Figure 6C). Increasing noise levels, surprisingly, led to a disappearance of interference effects. Reducing the size of the hippocampal layer, on the other hand, increased the size of interference effects substantially, while leaving overall memory performance relatively intact. Both of these results are discussed in the additional material on the authors' Web site.

COMMENT

In this study, an integrated model of the MTL was used to elucidate differential contributions of the parahippocampal gyrus and hippocampus proper to episodic memory. In the model, dual sensory processing pathways, conveying object-based and contextual aspects of an episode, converge on the hippocampal formation, where a representation of their co-occurrence is stored. The function of the parahippocampal region in the model is to cross-associate the information in the 2 input streams. In line with previous studies, the hippocampal module is required to quickly store the co-occurrence representations while enhancing pattern separation.[34,48] As shown in the current and in previous studies, these 2 aspects of memory processing rely on different network characteristics and, thus, are most efficiently subserved by dedicated circuitry.[32]

Although the model incorporates only crude principles of MTL organization, it captures several realistic features of human memory. For instance, retrieval is highly context sensitive; sampling with a context cue elicits few intrusions and false alarms. Furthermore, even small differences in context can discriminate between episodes incorporating the same item, for instance, in the AB-AC paradigm, where correct episodes are retrieved with small, albeit significant, interference effects.

While we tuned the model to replicate normal memory function, MTL abnormalities and their effects on performance were investigated in a principled manner. Out of various *in silico* lesions, only reduced wiring of the parahippocampal region and its hippocampopetal projections produced the memory deficit profile observed in schizophrenia. This manipulation led to compromised cross-association of episodic features and a superimposed, mild reduction of pattern separation in the system. The latter malfunction made some patterns irretrievable, affecting all memory tasks including recognition, and leading to what has been interpreted as an encoding deficit. The cross-association problem hampered "searching" of the memory store. This preferentially affected tasks with a large retrieval demand, such as free recall, leading to what has been interpreted as a retrieval deficit. In fact, our results indicate that both manifestations of memory impairment are due to abnormal encoding.

The reduced parahippocampal connectivity also led to a shift in the balance of inputs on the entorhinal layer,

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in favor of top-down ones. Thus, the system became biased to reinstate stored patterns, even when these were not associated with the online sensory input cues. This contributed to the increase in false-positive memories and intrusions. However, this network abnormality may also underlie cognitive problems that are less obviously related to memory impairment.

Our model has interesting correspondences to models developed by McGlashan and Hoffman.[49] In their simulations, excessive pruning of connections in modules representing association cortex caused the network to produce percepts spontaneously, in the absence of input. They related these observations to formation of psychotic symptoms in schizophrenia. Their results and ours both suggest that altered connectivity may play an important role in the syndrome.

The model currently has several limitations. For one, it learns only associations between item and context, disregarding interitem associations. Furthermore, forgetting was not explicitly modeled, although some overwriting of older patterns by newer ones did occur. Finally, in the present model, the 2 putative process components of recognition, recollection and familiarity,[50-52] are only distinguished in a rudimentary manner (ie, retrieval via the hippocampal layer might reflect recollection, and direct activation by input nodes of associated entorhinal nodes may contribute familiarity). While implementing these features would make the model more general, there is no a priori reason to think that they would change the patterns in performance presented herein.

Finally, an important question for this model relates to the falsifiable hypotheses that it generates. The answer can be approached on 2 levels. First, the model could be falsified by neuropathological evidence in schizophrenia that MTL abnormalities are not due to connectivity. Second, it could be falsified through specific predictions about schizophrenic memory performance. For example, we demonstrated that what appeared to be disproportionate failures in retrieval were, in fact, failures due to compromised encoding. This leads to the testable prediction that the retrieval deficit should be relatively independent of circumstances at the time of recall. Our model may also be used to predict performance on aspects of episodic memory that have not yet been extensively characterized in schizophrenic patients. For instance, simulations are currently under way to predict effects of connectivity loss on source monitoring, familiarity, and word frequency effects in free recall and recognition.

In conclusion, we devised a model of MTL episodic memory function that was tuned to mimic normal performance in free recall, cued recall, recognition, and paired associate learning with interference. We then subjected our *in silico* model to a variety of lesions in a principled manner. We found decisive evidence that only massive losses in connectivity resulted in a "schizophrenia-like" profile of memory performance. From an information-processing standpoint, we also were able to demonstrate that what appeared to be disproportionate failures in retrieval were due to compromised encoding.

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Correction

Error in Byline. In the Original Article by Caton et al titled "Differences Between Early-Phase Primary Psychotic Disorders With Concurrent Substance Use and Substance-Induced Psychoses," published in the February issue of the ARCHIVES (2005;62:137-145), an error occurred in the byline on page 137. The byline should have read as follows: Carol L. M. Caton, PhD; Robert E. Drake, MD, PhD; Deborah S. Hasin, PhD; Boanerges Dominguez, MS; Patrick E. Shrout, PhD; Sharon Samet, MSW; Bella Schanzer, MD." The journal regrets the error.

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