



A computational approach to memory deficits in schizophrenia

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Abstract

Episodic memory impairment is one of the most reliable neuropsychological findings in schizophrenia. It has been suggested that medial temporal lobe abnormalities in schizophrenia underlie this impairment. We suggest that the specific memory deficits in schizophrenia may be caused by abnormal hippocampo-cortical communication via parahippocampal areas. We have used connectionist simulations to investigate this notion. The simulations involve list learning in a model that incorporates characteristics of the hippocampal and parahippocampal region. In this model context is used to store and recall episodic memories. Reduction of the nodes in the parahippocampal module of the model resulted in a schizophrenia-like memory deficit profile. © 2002 Published by Elsevier Science B.V.

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1. Introduction

Memory impairment is one of the most reliable neuropsychological findings in schizophrenia. Review of the available data shows notable impairments in free recall, a lesser deficit in cued recall tasks and relatively spared recognition. These data suggest a mild to moderate deficit in encoding and an additional, more severe, deficit in retrieval of episodic information [2]. A less extensive body of evidence suggests normal forgetting in the range of minutes to hours [7]. This distinguishes the memory profile from the amnesias (e.g. in Alzheimer's disease and following hippocampal lesions), in which a highly increased forgetting on this time scale is observed.

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The above memory impairments appear to be a stable trait of schizophrenia, and do not show dependence on attention or other executive components of learning, as is the case in ‘frontal’ patients [11]. In view of the basic and stable nature of the memory impairments, we suggest that they may, instead, be related to medial temporal lobe dysfunction (MTL). This region has been implicated repeatedly in schizophrenia [6,15], showing reduced volume [18] and various signs of prenatal maldevelopment [8,15]. Within the MTL, volume reduction and cell loss are largest in the parahippocampal gyrus, particularly in the entorhinal cortex [3,15,18]. Volume reduction in the adjacent hippocampus proper appears rather to reflect reduced afferentiation and decreased size of principal cells [8].

The following presents a connectionist MTL model that accounts for standard memory paradigms in normals and suggests how hypoplasias in the parahippocampal region may produce the memory deficit profile observed in schizophrenia.

2. Rationale of the model

The differential episodic memory deficits in schizophrenia and amnesic syndromes suggest that the MTL circuitry subserves at least two, discernible, functions with respect to episodic memory: (1) fast, auto-associative learning and (2) integration of convergent sensory inputs, in a way that sustains efficient encoding, as well as retrieval of episodic memories. A defect in autoassociative learning would be expected to impair fast episodic storage altogether, resulting in amnesia-like memory problems. A large body of evidence has shown that this type of impairment results after damage to the hippocampus proper [13]. For the second putative function less clinical data is available. However, experimental evidence suggests that the parahippocampal region, consisting of the entorhinal, perirhinal and parahippocampal cortex, may be involved in sensory integration.

Anatomical data has shown that the bulk of cortical input to the hippocampus is segregated over two, largely non-overlapping, input streams [12]. One of these runs over the perirhinal cortex and lateral entorhinal area (LEA), the other over the parahippocampal cortex and medial entorhinal area (MEA). In primates, the former stream mostly receives visual object-related information, while the latter largely processes information from non-object, visuospatial areas [14]. In line with the anatomical findings, various papers show that the perirhinal cortex is involved in fast learning and recognition of objects [1,9], while the parahippocampal cortex may store memories for spaces and spatial relations [4,16]. In our model we hypothesize that the information conveyed by these two areas is integrated into an episodic trace in the pathways to the hippocampus, most notably in the entorhinal cortex and the dentate gyrus. We, furthermore, propose that the inputs to the hippocampus are not temporally equivalent. That is, the parahippocampal-MEA stream may detect more stable, context-like information, while the perirhinal-LEA stream may process relatively variable information. In partial support of this notion, neurons in the perirhinal cortex show fast and enduring adaptation to repeated stimulation [19].

In our view, the specific memory deficits in schizophrenia may be caused, not by abnormalities in the hippocampal auto-associative components of the circuitry, which would be expected to result in an increased forgetting rate, but rather by abnormalities in the parahippocampal region, disrupting the integrative function of the network. Our modeling efforts approach these matters by simulating a typical episodic memory task: list learning. The presented model simulates how two input streams may be integrated into episodic memories, which are stored through an orthogonalized compact code. Input patterns in the object stream can be reinstated by a process of cued recall. We test the hypothesis that a ‘hypoplasia’ of the integrative module in the circuit results in retrieval deficits.

3. The model architecture

The network used in the simulations consists of four modules: Link, ParaLink, and two input modules: ‘Item input’ and ‘Context input’ (see Fig. 1). Both inputs have widespread, random connections to ParaLink. This latter module, interposed between Link and the input layers, communicates representations of item-context associations up and down the hierarchy. ParaLink is biased, by feedback from Link, towards representation of previously viewed patterns.

The ParaLink module has highly plastic reciprocal connections with Link. The projection to Link is random; the feedback projection is full. Link serves to auto-associatively store patterns, created by parahippocampal activity, that can later be used to retrieve

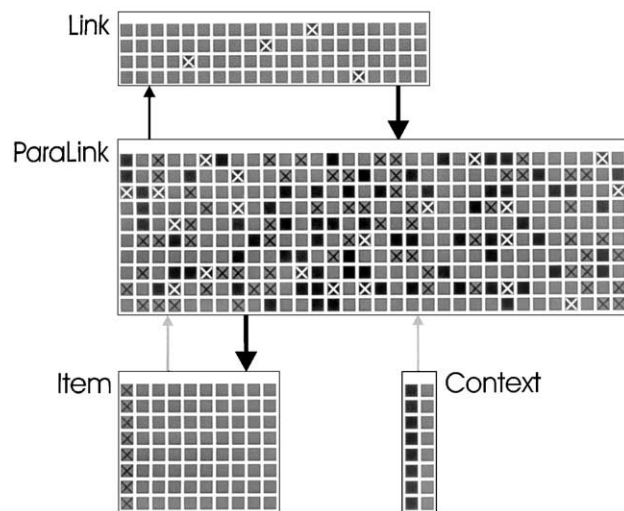


Fig. 1. Network model used in the simulations. Thin arrows represent random connections, thick ones are full. Black connections are plastic, gray ones are not. Crosses denote ParaLink nodes receiving inputs from the active context. Black nodes receive inputs from the active item nodes. ParaLink nodes in the intersection of item and context projection may come to represent the unique input combination (black nodes with a white cross).

patterns in ParaLink. ParaLink nodes send a full projection back to the Item input layer. This connection learns the relation between ParaLink patterns and item patterns. The summed input to the nodes of an item pattern constitutes the output of the model.

Both higher-level modules have linearly summing threshold nodes with firing governed by k -Winner-Take-All dynamics. Segregation of the autoassociative Link layer and the integratory ParaLink is necessary to insert an orthogonalization step between the two. Without this orthogonalization there is preferential learning of pattern overlap and formation of spurious patterns that are always recalled. Hence, performance drops dramatically when Link and ParaLink are fused into a single recurrent layer (results of simulation not shown). The model was built using the Walnut/Nutshell software [10].

4. Modeling list learning

In the simulations we present the model with a sequence of 10 items, while one context is activated. During learning, the connections from Link to ParaLink are modulated so that transmission is low. Hence, activity in the system is mostly determined by the inputs from Item and Context. In ParaLink, nodes in the intersection of projections of the active inputs are activated (Fig. 1). This pattern then activates nodes in Link. The resulting patterns in ParaLink and Link are stored in the reciprocal connections between the two layers. Moreover, the ParaLink pattern is associated with the activated item representation via learning feedback connections from ParaLink to the Item module.

Following the learning session, transmission in the feedback connection from Link is restored and retrieval is tested under various cueing conditions (Table 1). Cueing consists in partial activation of item and/or context representations. If, during 100 iterations, a pattern is retrieved to criterion (80% of maximum feedback) at least once, it is counted as recalled. Each time the criterion value is reached, Link and ParaLink nodes are reset. To test the specificity of context cues, recall was also tested using an alternative context cue.

Recall occurs by a sampling process, in which patterns are partly activated by the cues and then completed by the Link module. As a consequence, the model occasionally gets stuck in a spurious pattern, particularly during free recall. Oscillations or slight amounts of random activity counteract this phenomenon, suggesting another rationale for oscillations in attractor networks.

Notably, the differential temporal patterning of the inputs poses constraints on connectivity. The more constant context input requires: (1) low output variance. Otherwise, representation of all items is biased toward those ParaLink nodes receiving strongest context input. (2) A denser projection than the Item module, in order to accommodate unique intersection patterns with multiple items. Hence, the respective likelihoods with which connections between the two input modules and ParaLink are formed constitute important model parameters.

Free recall, cued recall and recognition can plausibly be simulated with the present model. In free recall, the ‘normal’ model performs as a sample-and-complete network, where the context representation activates part of all learned item-context representations, and a specific item is selected by an interactive completion process operating

Table 1
 Cue size in the three simulated memory paradigms^a

Paradigm	Item cue	Context cue
Free recall	0	6/8
Cued recall	3/8	6/8
Recognition	6/8	6/8

^aValues represent cue impacts as proportions of the item or context nodes activated during learning.

in Link and ParaLink. The model is able to retrieve most list patterns in this way, in the given time. In recognition and cued recall, the item cue guides the search process. In recognition this leads to perfect retrieval of the correct item, while cued recall performance is intermediate between recognition and free recall.

5. Modeling developmental schizophrenia

A developmental hypoplasia was simulated reducing the ParaLink nodes by 50%. Developmental hypoplasia is likely to result in abnormal neural wiring. Hence, the model was tested in three ‘maldeveloped’ conditions, taking into account possible secondary effects of the hypoplasia on afferent projections and global inhibition: (1) while ParaLink is scaled down, the number of bottom-up input connections remains constant, leading to hyperinnervation. (2) ParaLink is downscaled keeping the number of active nodes in ParaLink (k) constant, resulting in hyperactivity. (3) Both input connections and global inhibition remain constant, while ParaLink is scaled down. To be complete we included a condition in which both k and the number of input connections were scaled down with ParaLink, so that neither hyperinnervation nor hyperactivity occurred. Effects of other manipulations are presently under investigation.

All manipulations involving hypoplasia or hyperactivity lead to lower recall performance (Fig. 2a). As in schizophrenia, the deficit becomes progressively more severe with increasing dependence of retrieval on context cues. The two manipulations affect memory performance by different mechanisms: with hyperinnervation, the mean number of inputs on ParaLink nodes increases, but so does input variance (the standard deviation in the number of connections one individual ParaLink node receives goes from 0.78 to 1.08). Due to the increased variance, more nodes in ParaLink patterns receive connections predominantly from a single input source, at the expense of nodes receiving combined input. Hence, single cues activate a smaller part of the learned pattern. Although in this situation learning of unique patterns in ParaLink and appropriate patterns in Link is spared, these patterns cannot be recalled via the context cue alone. Addition of (part-)word cues greatly improves simulated recall (Fig. 2a).

On the other hand, hyperactivity leads to increased pattern overlap in ParaLink, which, in turn, results in pattern overlap in Link and deficient encoding (Fig. 2c). During recall, spurious activation states can occur that do not result in item recall. Moreover, item cues can trigger recall irrespective of the activated context. Hyperactivation thus leads to a loss of context specificity (Fig. 2b).

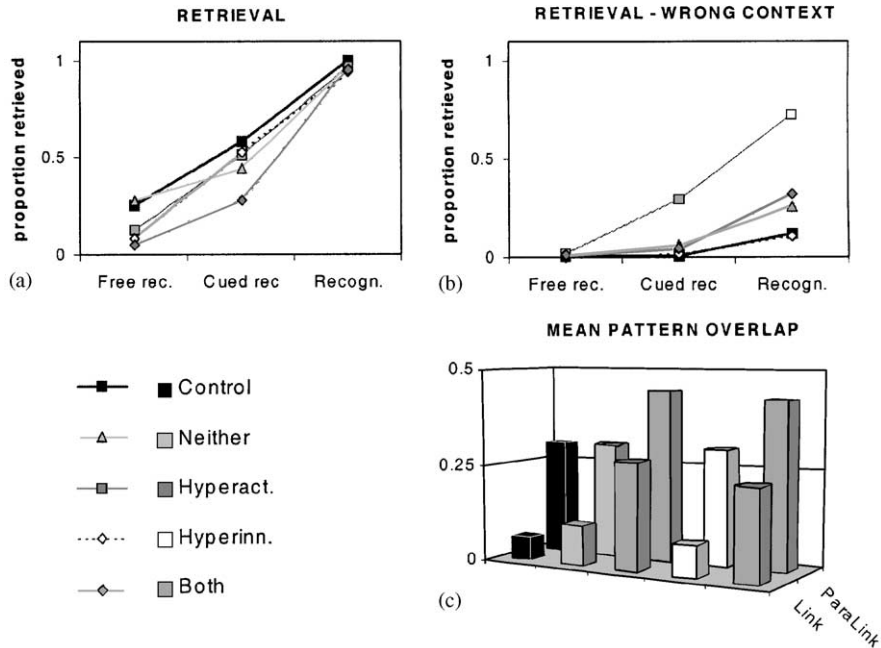


Fig. 2. Four hypoplastic conditions (see main text) were compared to a control simulation in which there was no hypoplasia. (a) Mean proportions of recalled items during free recall, cued recall and recognition over 25 replications. (b) Retrieval is tested, while cueing with an alternative (wrong) context, providing a measure of how much the model confuses context. (c) Mean pattern overlap in Link and ParaLink, respectively, in each of the model conditions.

6. Discussion

Episodic memory has not been studied extensively by connectionist models thus far. The present study suggests that an episodic trace consists in an association, based on co-occurrence, between object-related information and more stable context-like information. It was shown that such stored co-occurrence patterns can be used to retrieve patterns in the input sources, if the integration of input information respects the following principles: To represent as many unique input combinations as possible, the multiple input layers should emit extensive random projections to the integrator module. Hereby, more constant inputs require a denser projection and lower output variance than more variable ones, as more patterns need to be connected with the stable context than with the unstable item information.

As observed previously, various evidence supports the notion of parallel processing and pattern integration in the parahippocampal region. The integration of information conveyed by the two main processing streams (perirhinal-LEA and parahippocampal-MEA) might hereby occur not in one step, as in the simulated network, but over multiple synaptic steps. For instance, partial integration may occur at the level of the

entorhinal cortex, through limited overlap of the projections from the perirhinal and parahippocampal cortices [5]. A second integration step may occur in granule cells of the dentate gyrus, which receive fully overlapping afferentiation from the LEA and MEA [17]. The connectivity constraints investigated in our model may apply at each integration step.

Various findings suggest that schizophrenia neuropathology preferentially concerns the parahippocampal region [3,6,8,15,18]. In our model, ‘hypoplasia’ of the integratory layer led to a substantial deficit in free recall and a lesser impairment in cued recall, while recognition was relatively spared. These results suggest that similar memory deficits observed in schizophrenia may result from defective integration of multiple inputs into an episodic trace. The model, furthermore, predicts that schizophrenic memory performance should deteriorate with increasing reliance on any ‘single source’ cue. For example, schizophrenic subjects should exhibit less priming from new associations than normal subjects.

The combined findings with this model support the notion that the process of input integration is crucial for normal episodic retrieval and that defects may result in schizophrenia type memory deficits.

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