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ScienceDirect
Schizophrenia Research 89 (2007) 177–190
SCHIZOPHRENIA RESEARCH
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Modeling of context-dependent retrieval in hippocampal region CA1: Implications for cognitive function in schizophrenia

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Received 17 January 2006; received in revised form 10 August 2006; accepted 11 August 2006
Available online 20 October 2006

Abstract

The symptoms of schizophrenia may be associated with reductions in NMDA receptor (NMDAR) function. This is suggested by the psychotomimetic effects of NMDA antagonists, the ameliorative effects of NMDAR indirect agonists, elevated levels of the NMDA antagonist *N*-acetyl-aspartyl-glutamate (NAAG) in schizophrenic brain, and findings from recent genetic studies. However, the link between reduced NMDAR function and the behavioral features of schizophrenics has not been made explicit. Here we present a network simulation of hippocampal function, focused on retrieval of verbal stimuli in human memory tasks. Specifically, we trained a computational model of the hippocampal complex to perform a context-dependent paired associate task, a free recall task with category clustering, and the transitive inference (TI) task. In this network, direct perforant pathway input from entorhinal cortex to region CA1 provides the basis for semantic context cueing during initial encoding and retrieval, allowing selective retrieval on the basis of category cues. Alterations in the magnitude of this direct perforant pathway input to region CA1 causes impairments in use of organizational strategies for memory, accounting for specific features of memory dysfunction in schizophrenics and in normals treated with ketamine. This model provides a theoretical link between cellular physiological changes and specific cognitive symptoms. As such, it can shed light on the etiology of schizophrenia in a fundamental way, and also holds the promise of pointing the way to more effective treatments.

Keywords: Hippocampus; NMDA; Computational model; Context; Memory; Semantic tasks

1. Introduction

The symptoms of schizophrenia may be associated with endogenous reductions in NMDAR function. Drugs which block NMDA receptors cause psychotomimetic symptoms in normals and enhance symptoms in schizophrenics (Newcomer et al., 1999; Javitt and Zukin, 1991; Malhotra et al., 1997). NMDA hypofunction in schizophrenics may be caused by antagonism of

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0920-9964/$ - see front matter.
doi:10.1016/j.schres.2006.08.007

NMDA receptors due to pathological levels of *N*-acetyl-aspartyl-glutamate (NAAG). Studies have shown reductions of glutamate carboxypeptidase II (GCP II) (also known as NAALAdase) the enzyme which breaks down NAAG, in postmortem studies of schizophrenic brains (Tsai et al., 1995). Studies have also shown reductions in NAA, the enzymatic metabolite of NAAG in schizophrenic brains (Bertolino et al., 1998). If NMDA hypofunction is an element in the negative and cognitive symptoms of schizophrenia, then activation of the NMDA receptor may have therapeutic effects. In fact, studies have shown reduction of negative symptoms in schizophrenia with substances which act at the glycine modulatory site (GMS) on the NMDA receptor, including substances such as glycine (Heresco-Levy et al., 1999), D-serine (Tsai et al., 1999) and D-cycloserine (Goff et al., 1995, 1999).

These potential connections between NMDA receptor blockade and the cognitive symptoms of schizophrenia are fascinating, but have not been made explicit in circuit level models of cortical function. The effects of NMDAR hypofunction have the potential for causing selective alterations in functional connectivity within the hippocampal system (Grunze et al., 1996). One potential site for this influence is the direct input from entorhinal cortex to stratum lacunosum-moleculare in region CA1. This excitatory input shows greater reductions after blockade of NMDA receptors than does the excitatory input from region CA3 terminating in stratum radiatum (Otmakhova et al., 2002). In addition, the multiplicative interaction of the inputs to stratum lacunosum-moleculare and stratum radiatum may depend upon these NMDA receptors. Subtle antagonism of NMDAR function caused by reduced GMS occupancy could cause a striking decrease in the magnitude of entorhinal influence on region CA1. As an additional potential factor, NAAG is a potent agonist at mGlu3 receptors (Wroblewska et al., 1997); these mGluR3 receptors have been shown to inhibit excitatory synaptic transmission at this perforant pathway input to region CA1 (Kew et al., 2001).

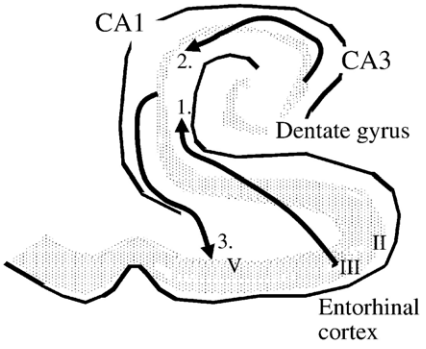


Fig. 1. Schematic of hippocampal connectivity, showing connections which are the focus of the modeling. One population of computational units represents the activity of neurons in entorhinal cortex layer III, which provides afferent glutamatergic input to hippocampal region CA1 (1). Another population of units represents the glutamatergic pyramidal cells of region CA3, which receive inputs from entorhinal cortex and dentate gyrus, and send excitatory recurrent connections to pyramidal cells in region CA1 (2) as well as other cells in CA3. Finally, a separate population of units represents the glutamatergic pyramidal cells of region CA1 which receive convergent input from region CA3 and entorhinal cortex. Input from region CA3 arrives via the Schaffer collaterals (2) which terminate on proximal dendrites of CA1 cells in stratum radiatum, and input from entorhinal cortex layer III arrives via the perforant path fibers (1), which terminate on distal dendrites of CA1 cells in stratum lacunosum-moleculare. Most sensory input entering the hippocampus arrives via entorhinal cortex, which receives convergent input from multimodal association cortices. Output to cortical structures projects via deep layers of entorhinal cortex (3).

The direct entorhinal input to region CA1 has been proposed to allow a comparison function to be performed in region CA1 (Gray, 1982; Eichenbaum and Buckingham, 1989; Levy, 1989; Hasselmo and Schnell, 1994; Hasselmo, 1995; Lisman and Otmakhova, 2001; Hasselmo et al., 2002). It has been suggested that this comparison function could serve a number of different roles (Hasselmo and Schnell, 1994; Hasselmo et al., 2002). Here we propose that direct entorhinal input to region CA1 represents the specific temporal context of episodic associations, where "temporal context" means the memory of the specific time that a cognition or percept was encoded (Howard and Kahana, 2002). This allows an interaction of item-to-item association with the specific temporal context in which these associations occurred. In as much as temporal context carries semantic information, this interaction could be important for aspects of verbal memory function. In particular, it could mediate the effect of semantic cueing on verbal memory encoding and retrieval, which can enhance the encoding, cued recall, and free recall of lists of words by control subjects in tasks such as the California Verbal Learning Task (CVLT) or other tasks using semantic cues for retrieval. Research on schizophrenic patients has shown that semantic cues provide less of a benefit for verbal memory retrieval by schizophrenics compared to controls (Kareken et al., 1996; Brebion et al., 1997; Hill et al., 2004). Interestingly, subjects under the influence of the NMDA receptor blocker ketamine also show a reduction in the effect of semantic cues on retrieval performance (Newcomer et al., 1999). The interaction of item and context associations in region CA1 could also be important for encoding and retrieval of transitivity and transitive inference (Dusek and Eichenbaum, 1997). Impairments of this interaction could

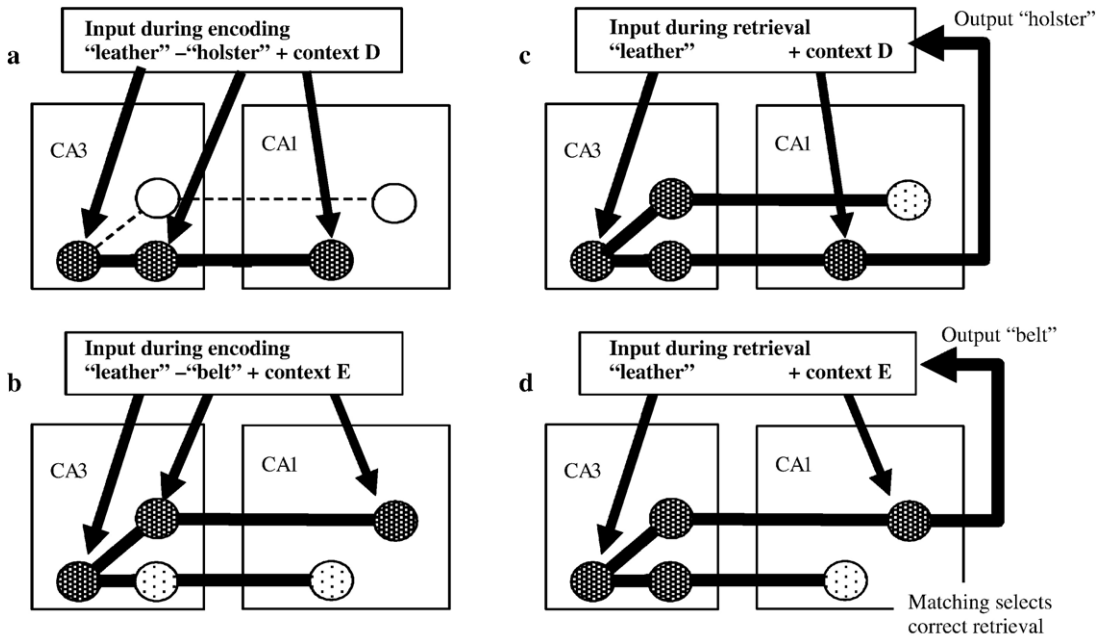


Fig. 2. Summary of the potential role of entorhinal cortical input to region CA1 in context-dependent retrieval. Encoding: (A) Within region CA3, activity in a subset of neurons representing the word "leather" in this episode occurs at the same time as activity in a subset of neurons representing the word "holster." In the figure, each of these populations is just represented with a single circle, and the activity is represented by shading of the circle. As this input repetitively activates the neurons, the processes of synaptic modification gradually increases the efficacy of synapses between these two sets of neurons, as illustrated by the thicker line between the two circles. This is consistent with evidence that long-term potentiation of the excitatory recurrent connections terminating in stratum radiatum of region CA3 has Hebbian properties. That is, the individual synapses are strengthened dependent on simultaneous pre- and post-synaptic activity (see reviews in Bliss and Collingridge, 1993; Bi and Poo, 1998; Levy and Steward, 1983). This is followed by storage of an association between the specific words and the episodic context D, arriving in region CA1 from entorhinal cortex. (B) Storage of an additional association between the cue word (leather) and another word (belt) may involve overlapping representations in region CA3. This second association can be disambiguated by the association with a different episodic context (E), arriving in region CA1 from entorhinal cortex. Retrieval: (C) The experimenter gives the first word (e.g. "leather") as a cue. This will evoke some activity in the entorhinal cortex, which will spread into region CA3, and here the population of neurons associated with the word "leather" becomes active. Presentation of the cue word "leather" activates both associated words ("holster" and "belt"), and then the cue for context D allows selective retrieval of the correct associated word ("holster"). (D) Similarly, presentation of the cue word "leather" with a cue for context E allows retrieval of the correct associated word ("belt"). Thus, entorhinal input to region CA1 can provide context-dependent gating of the retrieval from the hippocampus.

underlie the transitive inference deficit in schizophrenia (Titone et al., 2004).

2. Methods

The simulations presented here are based on computational models of hippocampus employed by the authors in a number of previous studies and described in the literature (e.g. Hasselmo and Wyble, 1997; Hasselmo et al., 1995; Hasselmo and Schnell, 1994). The reader is referred to supplementary materials for details of the modeling approach.

The models used in this paper employed a combination of different computational techniques to address the circuit level interactions within the hippocampal formation and associated cortical structures. In one set of models, continuous firing rate representations of neurons are used to model the interaction of populations of neurons, using techniques similar to many existing models of the role of hippocampus in human memory function (Treves and Rolls, 1994; Hasselmo and Wyble, 1997; Rolls et al., 1997; O'Reilly et al., 1998; Norman and O'Reilly, 2004; Meeter et al., 2004; Talamini et al., 2005). These were programmed using the MATLAB simulation package. In a second set of models, more detailed circuits utilizing integrate- and-fire neurons allow analysis of unit response data from the simulation in a manner similar to that used for analysis of unit data in experimental preparations. In these simulations, the CATACOMB simulation package (Cannon et al., 2002; Hasselmo et al., 2002; Koene et al., 2003) was used.

Both models focus on the interaction of specific subregions of the hippocampal formation and adjacent entorhinal cortex via glutamatergic synaptic transmission.

A detailed description of the manner in which information flows through the simulated hippocampus—that is, the connectivity of the various modules of the system—is given in Fig. 1. A percept is represented as a particular pattern of activation of the neurons of a hippocampal module. Please see the online Supplementary Material for additional information on the computational modeling approach as well as details of its implementation.

3. Results

3.1. Background: episodic associations in hippocampus and context dependence

Hippocampal region CA3 has broadly distributed excitatory recurrent connections. These have been proposed—originally by Marr (1971)—to provide a system of connections ideal for encoding arbitrary, item-to-item associations between elements of an episodic memory. The convergent inputs to hippocampal region CA1 may provide a mechanism for the interaction of temporal context and item-to-item associations. The proposed mechanism of context-dependent retrieval is described in detail in Fig. 2. This extends the basic mechanism of storing associations between pairs of items, to address how a specific episodic association learned in a specific context can be retrieved. Specifically, it is proposed that the direct entorhinal cortical input to region CA1 can select which neuronal population in region CA1 becomes active, thereby regulating context-dependent retrieval.

If the direct entorhinal projection to region CA1 mediates context-dependent retrieval, any physiological alteration in this direct entorhinal projection will alter the nature of the context-dependent retrieval. Importantly, the direct entorhinal projection to region CA1 may have a specific sensitivity to alterations in NMDAR function. A number of physiological studies have demonstrated differential involvement of NMDA receptors in synaptic potentials elicited at different synaptic inputs to region CA1. The direct entorhinal input terminates in stratum lacunosum-moleculare (s. l-m) of region CA1. Stimulation of this input causes synaptic potentials with a greater NMDA receptor component than synaptic potentials elicited by stimulation of stratum radiatum (s. rad.) (Otmakhova et al., 2002; Otmakhova and Lisman, 2004). More recently, it has been demonstrated that NMDA

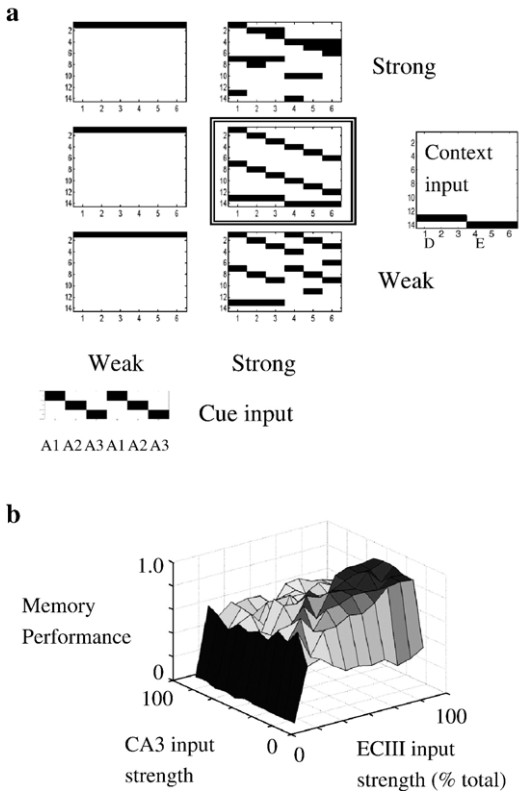


Fig. 3. Memory performance as a function of different strengths of input from region CA3 (Schaffer collateral input to stratum radiatum of region CA1) and different strengths of input from entorhinal cortex layer III (perforant path input to stratum lacunosum-moleculare of region CA1). (a) Activity in region CA1 during context input from ECIII (D versus E) and cue input from region CA3 ("first words" A1, A2, A3). Each rectangle shows the activity of different units in region CA1 plotted vertically with time plotted horizontally. The pattern of activity of the neurons in CA1 represents the responses of the system (the "second word") after it is cued with the first word. For example, when the hippocampal model is cued with A1 in context D, the desired response is a pattern in CA1 consisting of activation of neurons 1, 7, and 13. When the hippocampal model is cued with A1 in context E, the correct response is activation of neurons 4, 10, and 14 in CA1. When parameters are set for best performance (double rectangle around plot), the region CA1 activity shows effective sequential context-dependent retrieval of each of the individual items from the first context D followed by retrieval of the items from the second context E. The activity in different rectangles of the figure shows region CA1 activity during recall for different parameter values. The strength of the entorhinal input to CA1—that is, the strength of the signal encoding *contextual* information—is varied for different rectangles on the vertical dimension, with strong context at top and weak at bottom. The strength of *cue* (CA3 input to CA1) is varied along the horizontal dimension, with weak at left and strong at right. A strong cue is necessary for retrieval (right side). When context is too strong, it causes repetitive activation of items from the same context (top right). When context is too weak, it allows repetition of the same items in different contexts (bottom right). Context must have an appropriate intermediate value for effective function. (b) Memory performance as a function of CA3 and ECIII inputs. Memory performance measure (as defined in text) is plotted on the vertical axis for different strengths of input from Region CA3 and entorhinal cortex layer III, as shown in the *xy* plane.

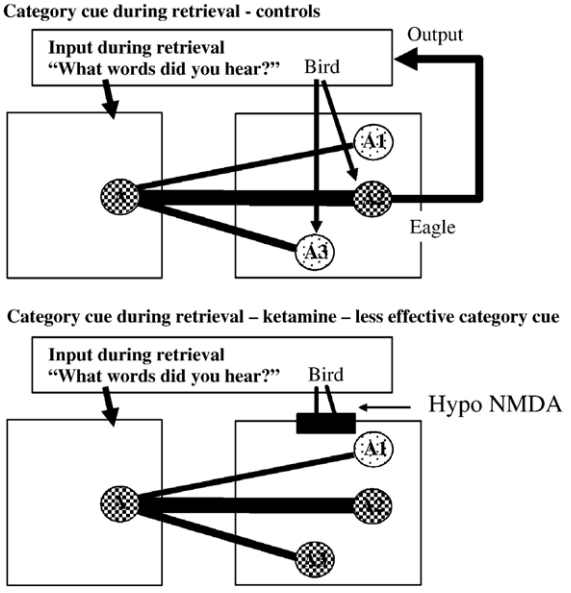


Fig. 4. Influence of category cue on retrieval in controls and schizophrenics. The top diagram illustrates how the category cue "bird" can assist in retrieval by providing a category context for gating the retrieval of individual words, such as "eagle." The bottom diagram shows how a reduction in NMDAR function at the perforant path input to region CA1 ("Hypo NMDA") reduces the influence of context (category) on retrieval in region CA1, preventing the enhancement of retrieval by presentation of a category cue.

receptors provide a multiplicative (supralinear) interaction of synaptic potentials stimulated in these two layers. This multiplicative interaction provides exactly the mechanisms ideal for gating of the output of the hippocampus, by allowing the response of neurons in CA1 to depend strongly on how well s. rad. input matches the convergent input from entorhinal cortex to s. l-m.

3.2. Impairments of context-dependent retrieval in schizophrenia

We used the model of context-dependent retrieval described above to model specific memory impairments associated with schizophrenia and with blockade of NMDA receptors by the antagonist ketamine. This modeling simulates the effect of selective reductions of entorhinal inputs to s. l-m. The effect of these reductions can be demonstrated in specific features of cognitive tasks which have been seen to be altered in schizophrenics and in normal subjects under the influence of the ketamine (Newcomer et al., 1999). In particular, studies have shown that schizophrenic patients demonstrate a large number of intrusions from previously learned pairs A–B when tested on new overlapping pairs A–C (Elvevag et al., 2000b). Elvevag et al counted the number and type of errors made by study participants and found that schizophrenics made significantly more intrusion errors than controls. In the version of the task employing moderately semantically related word pairs, these error rates were 2.69 for schizophrenics and 0.93 for control subjects ($p=0.05$). Because schizophrenic patients made a large number of errors of all types, intrusion type errors, when taken as a fraction of total errors, were similar in patient and control groups (45% vs. 50% respectively). This does not diminish the importance of this finding: intrusion errors are likely a special class of error indicating a particular deficiency in semantic processing, and the fact that their rate is increased in absolute terms is meaningful.

The performance of context-dependent paired associate retrieval in our model is shown in Fig. 3a. This figure shows retrieval after encoding with different strengths of region CA3 input to region CA1, and with different strengths of entorhinal layer III input to region

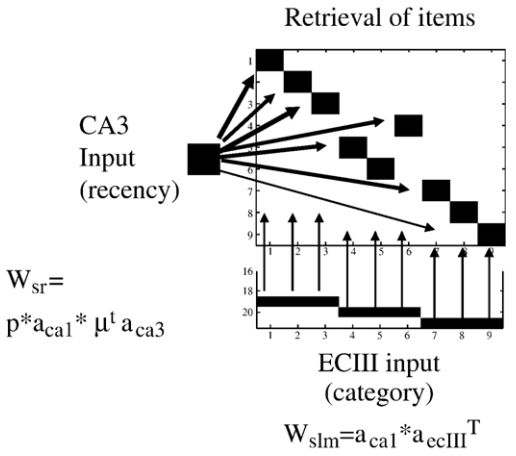


Fig. 5. Schematic representation of the simulation of free recall. During encoding, associations of variable strength are formed between the current item and each item from the list, allowing region CA3 activity to drive retrieval of all words on the list. Here, input from CA3 stays the same during retrieval, with variation in strength to different items depending on the recency of the item. Note that $\mu<1$, so that items presented earlier in the sequence receive greater weighting. Width of arrow is proportional to strength of association. In addition, category features in entorhinal cortex layer III are associated with each item. This allows temporal context to drive the retrieval of individual items in region CA1. For example, if three words from the category "bird" are presented sequentially, they will share the category representation in layer III, allowing an association between this category and the first three episodic representations. This figure shows three categories in layer III with three items in region CA1 for each category. (The retrieved word is represented by the activity of a single neuron in CA1, represented by a black box in a particular row.) Note that in free recall, items do not need to be retrieved in the same order as they were encoded, so the list need not be diagonal. Please see online Supplementary Materials for definitions of variables in equations.

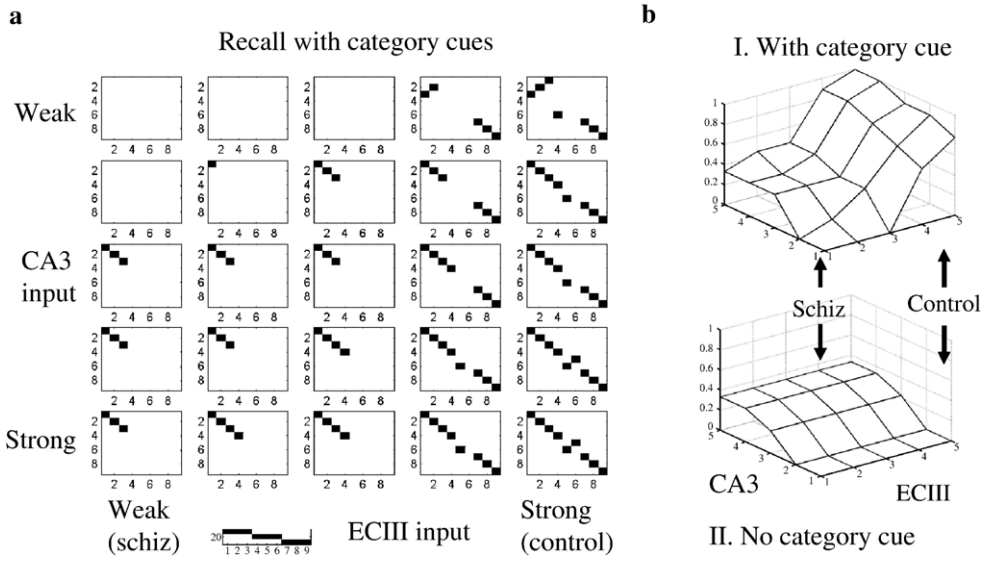


Fig. 6. (a) Free recall with semantic cues for different strengths of input from region CA3 (weak at top, strong at bottom) and entorhinal cortex layer III (weak at left, strong at right). Note that when ECIII input is weak (schiz), the network shows poor overall free recall (fewer rectangles indicate less retrieval) and it shows no benefit from category cues or semantic organization. In contrast, when ECIII input is strong (controls), the network more effectively retrieves multiple items from the list, consistent with the enhancement of memory in control subjects by category cues or semantic organization of the list. (Note that in free recall, items do not need to be retrieved in the same order as they were encoded, so the list need not be diagonal). (b) Memory performance with and without category cues. Memory performance is shown on the vertical axis as a function of different strengths of input from region CA3 and ECIII (horizontal plane). When ECIII input is weak (left), the network shows poor performance in both conditions, with little enhancement from category cues. In contrast, when ECIII input is strong (right), the network shows a clear enhancement of performance when category cues are provided (top) relative to their absence (bottom).

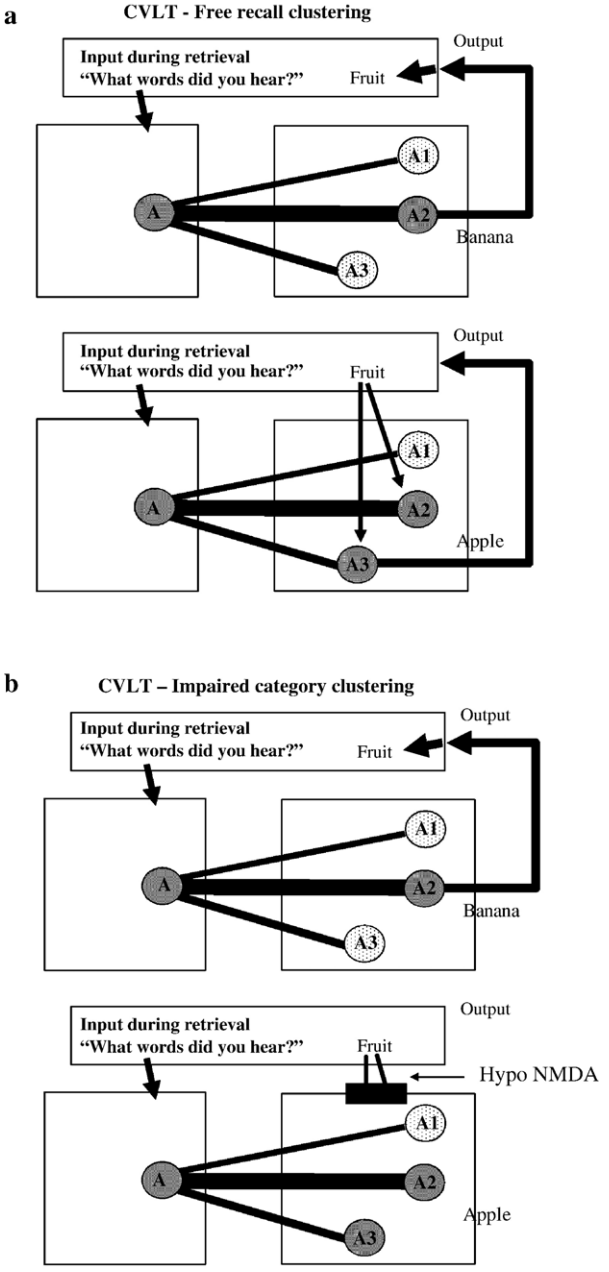
CA1. The quantitative properties of retrieval are shown graphically in Fig. 3b. These plots illustrate the importance of context in the recall process. Specifically, they show that the retrieval process requires the entorhinal layer III input—which represents the context in which the association was made—to be moderately strong. In particular, if this input is too weak, then the cued item input from region CA3-representing retrieval based on the cue word in a paired associate learning task—causes serious intrusions from prior learning. Schizophrenic patients showed a large number of intrusions from prior learning in a paired associate learning task (Elvevag et al., 2000b), consistent with this potential effect of reduced synaptic input from entorhinal cortex layer III input to region CA1.

3.3. Category effects in free recall

In free recall, semantic organization of the memorized words usually enhances retrieval. For example, if words in a list can be divided into groups of words with shared categories, this assists in retrieving the stored words. We chose this kind of recall task, instead of free recall of unrelated word lists, because the focus of our study was on understanding how hippocampus uses semantic information to encode memories, and how this may go awry in schizophrenia. Moreover, compromised performance on free recall of *unrelated* word lists does not appear to be specific to schizophrenic illness, having been seen in depression (Query and Megran, 1984; Austin et al., 1992; Uekermann et al., 2003), bipolar disorder (Ferrier et al., 1999; Krabendam et al., 2000), Alzheimer's Disease (Randolph et al., 1998; Woodward et al., 1999), and alcoholism (Query and Megran, 1984; Uekermann et al., 2003).

A number of studies have demonstrated a reduced influence of semantic organization on memory encoding and retrieval in schizophrenics (Kareken et al., 1996; Brebion et al., 1997; Hill et al., 2004) or subjects under the influence of the drug ketamine (Newcomer et al., 1999; Newcomer and Krystal, 2001). Indeed, many studies have shown that, in general, schizophrenics have difficulties in tasks with a semantic component, such as those testing semantic fluency, semantic priming, or semantic memory (Clare et al., 1993; McKay et al., 1996; Paulsen et al., 1996; Goldberg et al., 1998). However, there are also studies that indicate some types of memory tasks requiring semantic processing are essentially normal in schizophrenics (Paul et al., 2005). While a full discussion of this

complex question is beyond the scope of this paper, a possible reconciliation of these findings has been suggested by Paul et al. (2005): it is possible that schizophrenics perform normally in tasks which *force* subjects to semantically categorize words, such as those requiring the encoding of items to different "depths" (that is, superficial [perceptual] vs. deep [semantic/conceptual]); but when autonomous selection of efficient encoding strategies is required (as in free recall tasks) they perform more poorly.



Hippocampal mechanisms thought to underlie context-dependent retrieval in the free recall task are illustrated in Fig. 4. The manner in which we instantiated the task computationally is shown in Fig. 5. During encoding, connections of variable strength (according to recency) are made between the activity state in CA3 and different item representations in region CA1, as shown in the Figure. Simultaneously, during encoding, the category representation in entorhinal cortex layer III is associated with each item. This allows temporal context (i.e., category) to drive the retrieval of individual items in region CA1. This figure shows three categories with three items in each category.

The strength of entorhinal cortex layer III (ECIII) input determines how much category cues influence memory performance, as shown in Fig. 6, and also determines the overall efficacy of free recall. With strong ECIII input, category cues have a significant influence on performance, providing strong performance on the right side of Fig. 6a (controls), compared to the performance without category cues. This can be seen graphically in Fig. 6b, which shows a big difference in performance on the right side of the top and bottom plot (control subjects)—the condition with category cues (I) on top shows much higher performance than the condition without category cues (II) on the bottom. In contrast, with weak ECIII input, category cues do not have a significant influence on performance. The performance with weak ECIII input (schiz) on the left side of Fig. 6a is poor, and does not improve when category cues are provided. This is shown on the left side of the plots in Fig. 6b (schiz subjects), which show little difference in performance between the condition with category cues (I) on top and the condition without category cues on the bottom. This provides a potential functional explanation for the

Fig. 7. Role of retrieved category in gating subsequent retrieval, thereby resulting in category clustering. (a) Baseline (normal) condition. The top diagram shows how retrieval of one word from episodic memory (banana) activates the representation of context in entorhinal cortex, in the form of a category representation (fruit). The bottom diagram shows how this category context then gates further retrieval from episodic memory, causing the next retrieval to be a word from the same category (apple). This process results in category clustering. (b) Low-NMDA condition. The reduction in the NMDA contribution to perforant path input to region CA1 reduces category clustering. The top diagram shows that in these conditions, retrieval of one word can still activate the category (fruit) in entorhinal cortex. However, this context has a weaker influence on subsequent retrieval, due to the loss of the NMDA component of synaptic input from entorhinal cortex ("Hypo NMDA"). This is consistent with data from verbal memory tests of schizophrenic subjects (Keraken et al., 1996).

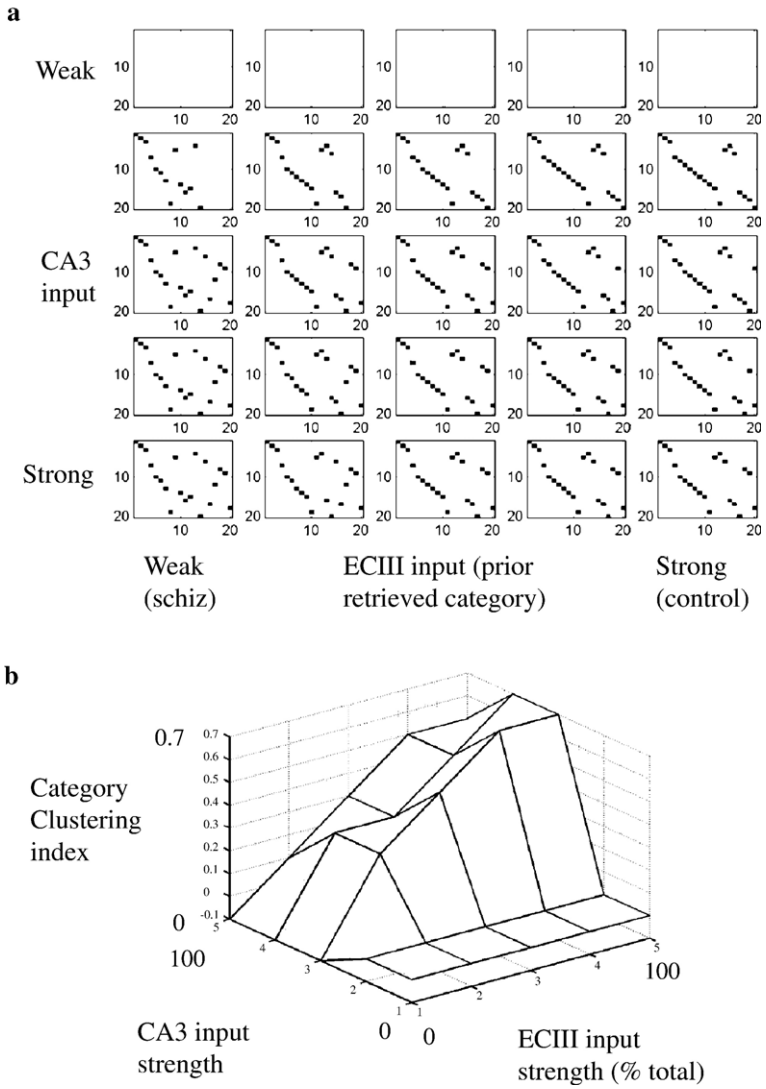


Fig. 8. Category clustering in the model with different strengths of CA3 and ECIII input. (a) With weak ECIII input on left (schiz), the previously retrieved item does not influence the category of subsequent retrieval, resulting in random jumps between different retrieved words, without sequential activation of words from a shared category. With strong ECIII input on right (controls), the previously retrieved item category does influence retrieval, resulting in frequent retrieval of a word from the same category as the preceding word, which appears as more sequential clustering of words. (b) Here, category clustering index (as defined in the Methods section) is shown on the vertical axis, and various strengths of CA3 and ECIII input are shown on the horizontal plane. Category clustering increases when ECIII input is strong (right).

weaker effect of semantic organization on memory retrieval in schizophrenics (Kareken et al., 1996; Brebion et al., 1997; Hill et al., 2004), and the weaker effect of semantic cues on memory function in subjects under the influence of ketamine (Newcomer et al., 1999). Note that the entire left side of Fig. 6a (with weak ECIII) shows poor overall free recall performance for all values of CA3 input. Fewer rectangles in each plot indicate less retrieval of individual words in free recall for the schizophrenia condition. Because ECIII input is shut off in this condition, this corresponds to an absence of category cues in the task, and indicates that retrieval in the schizophrenia condition would also be poor for unrelated words. Control subject performance for unrelated words is stronger if the category input is replaced with stronger episodic context from ECIII, linked uniformly or randomly with each of the encoded words, to allow stronger retrieval without the sequential category structure. The poor performance with weak ECIII is consistent with the poor overall performance of schizophrenic subjects on free recall tasks in both the presence and absence of category cues.

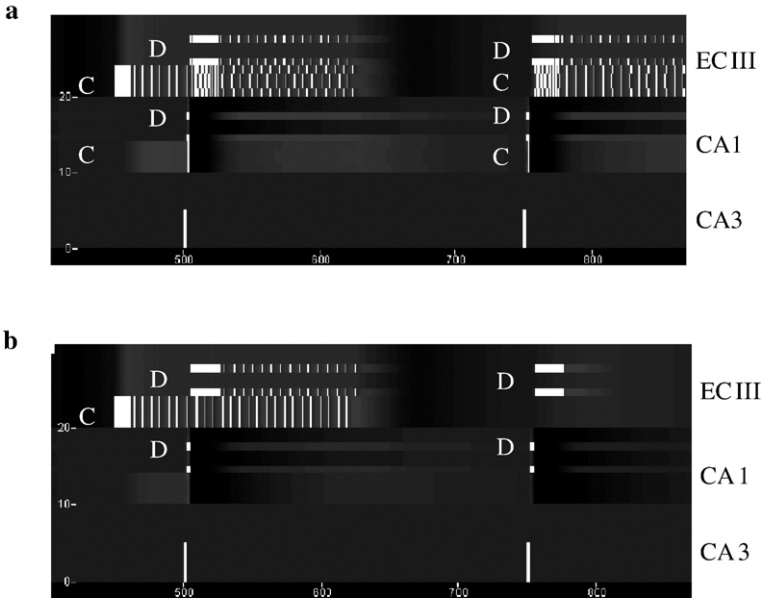


Fig. 9. Outputs of computational model that performs the transitive inference task. The key features of this network were a set of cells in EC with a strong after depolarization (Fransen et al., 2002; Koene et al., 2003) which therefore showed persistent firing when stimulated. The network was activated with an item pattern, which was presented to both EC and CA3 and a context pattern, which was presented only to EC. Input was provided from EC to CA1 by a one-to-one mapping representing the perforant path. A one-to-one connection was also made from CA1 to EC. The Schaffer collaterals were modeled as a random all-to-all mapping between CA3 and CA1, and were provided with Hebbian LTP. (a) Run of the intact model. Presentation of item pattern D (on the left side of Fig. 9a) was preceded by a context pattern, C, presented to EC. This context pattern in EC biased some units in CA1 that did not fire when presented with D alone. Because these conjunctive units were associated via Hebbian LTP with the representation of D in CA3, and CA1 was associated back to the context representation in EC, repetition of D (right side of the figure) results in recovery of the contextual state in EC by means of causing the conjunctive cells in CA1 to fire. (b) Run of the disrupted model. All features of this simulation were identical to the simulation shown in (a) except that the strength of the perforant path input from EC to CA1 was reduced in strength, simulating the effects of reduced NMDA receptor function (Otmakhova et al., 2002) or enhanced dopaminergic modulation on this pathway (Otmakhova and Lisman, 1999). Because the perforant path input to CA1 is weakened, cells in CA1 are not biased sufficiently to result in firing when activated by the item representation in CA3. As a consequence, there are no cells that respond to the conjunction of item D and context. Because these cells are not activated, they cannot activate their corresponding contextual units in EC and contextual retrieval fails (absence of spiking on right side of figure).

3.4. Category clustering of words

When normal subjects perform free recall, the generation of one output (e.g. apple) from a category, can result in generation of other words from the same category (e.g. banana, orange…). As illustrated in Fig. 7, the context-dependent retrieval model predicts that a reduction in the entorhinal input to region CA1 should reduce the phenomenon of category clustering in free recall.

We performed simulations to examine the process of category clustering due to context-dependent retrieval. In the example shown in Fig. 8a, weak ECIII input during encoding and retrieval results in relatively random generation of retrieved items from different categories. In contrast, when ECIII input is strong (controls), the retrieval of one word causes an active element for a shared category in ECIII. This shared category causes a greater propensity for retrieval of a subsequent word from the same category. This is visible as retrieval of items in clusters in the figure. Category clustering was quantified as shown in Fig. 8b, demonstrating a clear decrease in category clustering with weaker ECIII input as compared with the right side of the figure. These results are consistent with the hypothesis that reduced NMDA currents at the ECIII input to CA1 could underlie reduced semantic clustering during retrieval in the CVLT and a reduced effect of semantic cues on retrieval performance in schizophrenics (Kareken et al., 1996; Brebion et al., 1997; Hill et al., 2004).

3.5. Role of retrieved context in the transitive inference task

Previous work in rats has shown that ibotenic acid lesions of the hippocampus impair performance in specific variants of odor discrimination tasks (Bunsey and Eichenbaum, 1996), including performance on the transitive inference task using odor pairs (Dusek and

Eichenbaum, 1997). In this task, rats are trained on a series of premise pairs, in which one odor is always rewarded when presented with a specific other odor. This same process can be used to reward one odor in each of multiple overlapping pairs, where the rewarded odor is represented with a plus (+) sign and the unrewarded odor is represented with a minus (−) sign. The rat learns the premise pairs A–B+, B–C+, C–D+ and D–E+. The retrieval of the proper response to a single odor in these pairs is not impaired by hippocampal lesions, but such lesions do cause an impairment in the response to a probe pair such as B+D−, testing a relationship not previously tested. This is consistent with evidence from schizophrenic subjects, as shown in neuropsychological data from the Titone et al. (2004). In that study, nonverbal stimuli were used in a transitive inference task design. This study demonstrated significant impairments in performance on the B versus D premise pair by schizophrenics, but not by controls.

Much of the preceding simulations can be described as context providing the means to disambiguate recall of items. A related question is how items could be used to retrieve context, and whether this might be affected by dopamine hyperfunction. These questions can be addressed in light of the temporal context model (TCM), an ensemble-level model of episodic memory recall (Howard and Kahana, 2002). In TCM, a key feature ascribed to the hippocampus is the ability to cause item repetition to enable reconstruction of contextual states in EC. Howard et al. (2005) showed that a deficit in item-to-context learning caused an impairment in transitive (A–C) association while leaving pairwise (A–B, B–C) associations relatively unaffected. When a pair A–B is presented, B is associated to the context associated to A. When a pair B–C is presented later, B retrieves its original learning context, which includes elements of A. Thus, when item-to-context learning and contextual retrieval function normally, C is learned in a context that in essence includes A, resulting in transitive A–C associations.

Is it possible that reduced NMDA receptor function or enhanced dopaminergic modulation in schizophrenia could result in an impairment in item-to-context learning? Results of our simulations are shown in Fig. 9. Briefly, it was seen in the intact model that repetition of an item stimulus (labeled “D” in the figure) resulted in the recovery of the contextual state in EC by causing the conjunctive cells (that is, those cells that respond to the conjunction of item D and context) in CA1 to fire. This effect—and the ability to perform transitive inference—were absent in the disrupted, schizophrenic model.

4. Discussion

The simulation results presented here demonstrate the potential role of direct input from entorhinal cortex layer III for context-dependent retrieval within region CA1 of the hippocampal formation. Decreases in the strength of this direct afferent input to region CA1 cause impairments in the context-dependent retrieval of items. The decrease in strength of direct afferent input to region CA1 could occur in schizophrenia due to reductions in NMDA receptor activation, as NMDA receptors play a strong role in entorhinal input to region CA1 as opposed to region CA3 input (Otmakhova et al., 2002). Alternately, the decrease in strength of afferent input to region CA1 could occur due to excessive activation of dopaminergic receptors, as dopamine has been shown to suppress entorhinal input to stratum lacunosum-moleculare of region CA1 (Otmakhova and Lisman, 1999). While the precise role of dopamine in schizophrenic symptomatology is not entirely clear, a number of studies have suggested that the illness is characterized by a *hypodopaminergic* state at the cortical level (e.g., in the prefrontal cortex), and a *hyperdopaminergic* state at the subcortical (striatal) level (Abi-Dargham, 2004; Laruelle and Abi-Dargham, 1999). Recent work by Lisman and Grace (2005)—building on studies that have demonstrated dopaminergic projections to hippocampus (Gasbarri et al., 1997; Scatton et al., 1980) as well as significant presence of DA receptors in hippocampus (Gingrich et al., 1992; Huang and Kandel, 1995)—suggests that hyperdopaminergia in hippocampus also may contribute to the pathophysiology of the disease.

Simulations demonstrate how the reduction of entorhinal layer III input to region CA1 could cause impairments in paired-associate memory, reductions in the semantic category clustering in the CVLT task (Paulsen et al., 1995; Kareken et al., 1996; Hill et al., 2004), reductions in the usefulness of semantic cueing for recall in other verbal memory tasks (Brebion et al., 1997), and the impairment of transitive inference observed in schizophrenic patients. Decreased semantic clustering in the CVLT also appears in relatives of schizophrenics (Lyons et al., 1995) and also appears in tests of verbal fluency (Aloia et al., 1996). Neuroleptics have been shown to improve semantic priming effects in verbal fluency (Goldberg et al., 2000), which is consistent with the fact that neuroleptics reduce the suppression of entorhinal layer III input to region CA1 by dopamine (Otmakhova and Lisman, 1999).

One question that has been raised concerns the cerebral localization of the psychological tasks we have

modeled. For the CVLT, Johnson et al. (2001) examined this question indirectly by administering the test to a group of subjects who had previously been imaged using fMRI while performing a different (non-CVLT) verbal task. They found correlations between CVLT performance and activation on the earlier task in right hippocampus and right dorsolateral prefrontal cortex. Researchers who have correlated performance on the CVLT with volumes of various brain areas as measured by MRI in patients with Alzheimer's Disease (Stout et al., 1999; Kohler et al., 1998) and/or vascular dementia (Libon et al., 1998) found a positive correlation between performance on the exam and hippocampal volumes. Thus, while functional imaging studies that directly address this question have yet to be undertaken, it is apparent that hippocampus is crucially involved in CVLT performance, perhaps in conjunction with other brain areas. One early fMRI study of the transitive inference task (Acuna et al., 2002) showed activation in a number of brain areas, including premotor cortex, as well as inferior temporal cortices bilaterally. A subsequent imaging study (Heckers et al., 2004), however, also showed a similar pattern on non-transitive inference mnemonic tasks, and appropriate subtractions implicated anterior hippocampus (only) in TI tasks. The central importance of hippocampus in the transitive inference task has been corroborated in PET studies on human subjects (Nagode and Pardo, 2002) and lesion studies on laboratory animals (Dusek and Eichenbaum, 1997).

The impairments of context-dependent retrieval explored in the simulations presented here could provide a possible mechanism for impaired memory function in schizophrenics, which appears to affect tasks with an episodic memory component such as paired associate retrieval or cued and free recall more than tasks such as recognition memory. Schizophrenia patients are strongly impaired at paired-associate learning, even when given moderately related pairs (Elvevag et al., 2000b). Rushe et al. (1999) tested 58 schizophrenia patients and found large deficits in long-term story recall, paired associate learning, judgments of recency and conditional associative learning relative to controls. In contrast, they found modest or non-existent deficits in memory span and recognition memory.

In addition to the specific studies simulated here, there is other evidence that suggests that the memory deficit in schizophrenia is a consequence of an insensitivity to context, perhaps due to hippocampal disruption. Dreher et al. (2001) showed that schizophrenia patients were impaired recalling the temporal order in which stimuli were shown in a temporal recall task. Further, schizophrenia patients were impaired at recognizing spatial–temporal patterns. A perhaps related deficit was observed in schizophrenia patients who were presented with a list of words and asked to reconstruct their order (Elvevag et al., 2000a). Manschreck et al. (1997) studied recall of lists of words of varying contextual coherency. That is, one could construct lists of words that gradually approach written English by placing constraints on word order. Manschreck et al. (1997) argued that the difference between recall of controls and schizophrenia patients increased with the contextual constraints of the language, suggesting that schizophrenia patients do not benefit as much from contextual support as controls.

Other models of schizophrenia have focused on more general changes in synaptic connectivity within cortical structures as a possible pathological basis for the disorder (Ruppin et al., 1996; Greenstein-Messica and Ruppin, 1998; Hoffman and McGlashan, 2001; Siekmeier and Hoffman, 2002; Talamini et al., 2005). Another recent model proposes that a reduction in connectivity in particular parahippocampal pathways could underlie the pattern of memory impairments of the disorder (Talamini et al., 2005). The current study extends these previous studies by focusing on the dynamics at a particular set of neuroanatomic connections within the hippocampal region CA1. In so doing the computational framework presented here provides a theoretical mechanism for the interaction of context and item associations within region CA1, and will allow for exploration of the potential link between the verbal memory deficits observed in schizophrenia and magnitude of NMDA receptor activation at synaptic connections of entorhinal cortex terminating in region CA1 of the hippocampus. We believe the computational model we describe is compelling because it presents a "final common pathway" through which very different neurochemical abnormalities—decreased NMDA function and increased dopaminergic tone—could exert similar effects on verbal memory in schizophrenics. We do not claim that this constitutes "proof" of a particular theory. Rather, it represents a well-specified mechanistic hypothesis that can be examined and confirmed in future experimental work.

Acknowledgements

This research was supported by a Silvio O. Conte Center Grant for Neuroscience Research from the National Institute of Mental Health (MH60450).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2006.08.007.

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