

Hippocampal Function, Declarative Memory, and Schizophrenia: Anatomic and Functional Neuroimaging Considerations

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Current Neurology and Neuroscience Reports 2005, 5:249–256

Current Science Inc. ISSN 1528-4042

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Introduction

Memory permits an organism to bridge the past with the present, providing information about prior encounters with a stimulus or context that can serve to build predictive models for the present. At the neurobiologic level, it is well established that the hippocampus and surrounding medial temporal lobe (MTL) cortices play an essential role in declarative memory (*ie*, long-term memory for general facts and specific events) [1–5]. The MTL memory circuit is composed of multiple structures, including the hippocampal formation and the surrounding entorhinal, perirhinal, and parahippocampal cortices. The hippocampal formation is further composed of the dentate gyrus, the fields of the cornu Ammonis (CA), and subiculum. Recent investigations of MTL processing have sought to characterize the mnemonic function of specific MTL substructures. Hypotheses regarding functional segregation within the MTL have largely focused on the hierarchical connectivity of the region, emphasizing potential functional differences between the hippocampus and surrounding cortices [6–8]. Recent studies have also explored potential functional distinctions between substructures within the hippocampus, such as CA3 and subiculum [7–10].

Hypotheses regarding the functions of MTL substructures draw heavily on knowledge of the anatomic connectivity of the region with structures in neocortex, as well as information about the intrinsic connectivity within MTL. Such anatomically guided hypotheses may prove particularly insightful when investigating disease processes that affect MTL. Schizophrenia is associated with memory

impairments together with abnormalities in specific hippocampal substructures [11–14]. In particular, schizophrenic patients are impaired on declarative memory tasks [13,15], and functional neuroimaging studies have begun to reveal correlated hippocampal abnormalities. The present commentary reviews recent functional neuroimaging data regarding MTL function in the healthy brain and in schizophrenia. These initial observations are placed within the context of knowledge about projections to and within the MTL circuit, as anatomically informed models are likely to facilitate understanding of disease-related MTL dysfunction, potentially pointing to new avenues for intervention.

Medial Temporal Lobe Anatomy Cortical projections to and within the medial temporal lobe

Connections between hippocampus and entorhinal, perirhinal, and parahippocampal cortices are hierarchically organized [16]. Perirhinal cortex and parahippocampal cortex receive input from unimodal and polymodal association cortices in the lateral temporal, frontal, and parietal lobes by way of distinct pathways [17–21]. In infrahuman primates, the predominant inputs to perirhinal cortex come from unimodal visual association areas in the adjacent inferior temporal cortex, a region important for visual object processing [18]. In contrast, parahippocampal cortex receives its predominant input from posterior visual association areas and posterior parietal cortex, whose functions are more visuospatial in nature. Parahippocampal cortex also receives inputs from unimodal auditory association cortex in the superior temporal gyrus [18,19].

Perirhinal and parahippocampal cortices provide the major inputs to the second level of the MTL hierarchy (*ie*, entorhinal cortex), which also receives limited information from polymodal association areas [22]. The topographic organization of connections between these regions

and entorhinal cortex is distinct. Perirhinal cortex projects primarily to the anterior two thirds of entorhinal cortex, whereas parahippocampal cortical projections terminate primarily in the posterior third [23]. Parahippocampal connectivity with entorhinal cortex has a further topographic dimension—medial regions of parahippocampal cortex project to medial posterior entorhinal cortex, and lateral parahippocampal regions project to lateral posterior entorhinal cortex. Collectively, this pattern of connectivity suggests that the segregation of different neocortical inputs to perirhinal and parahippocampal cortices might be preserved within entorhinal cortex.

The entorhinal cortex provides the major inputs to hippocampus at the apex of the MTL hierarchy [20,24–27]. Information processed by hippocampus then descends back down the hierarchy through reciprocal connections and is distributed to neocortex through feedback projections. The higher-order memory representations formed by the structures of MTL thus have the capability of binding together information processed in multiple neocortical regions [16].

Hippocampal circuitry

Entorhinal cortex projects its output to the granule cells of the dentate gyrus by way of the polysynaptic (trisynaptic) pathway [16,28]. These dentate gyrus granule cells project to the CA3 region of hippocampus through the mossy fiber pathway. In turn, projections from the CA3 pyramidal cells include collaterals to other CA3 pyramidal cells comprising an extensive system of associational connections within the region. Projections from CA3 also include the Schaffer collaterals, which constitute the major projection to the CA1 pyramidal cells. CA1 also receives input from entorhinal cortex as part of the direct (monosynaptic) pathway [28,29]. CA1 then projects both to the subiculum and to entorhinal cortex. Unlike the CA3 field, there are few associational connections within CA1 [16].

It is noteworthy that, as with cortical projections to entorhinal cortex, projections from entorhinal cortex to hippocampus are topographically organized [26,27,29]. Lateral entorhinal cortex projects preferentially to posterior dentate gyrus, whereas medial entorhinal cortex projects to anterior dentate gyrus. Different anterior-posterior levels of entorhinal cortex also project to different proximal and distal regions of CA1 and subiculum. Given the topographic organization of inputs to entorhinal cortex from perirhinal and parahippocampal cortices, processing in different regions of dentate gyrus, CA fields, and subiculum may be influenced differentially by information from perirhinal and parahippocampal cortices [23]. Parahippocampal cortex, which projects more medially than perirhinal cortex [23], may influence more anterior regions of dentate gyrus. In addition, perirhinal and parahippocampal cortices terminate at different anterior-posterior levels of entorhinal cortex, suggesting a possible difference in the distribution of input from these regions to CA1 and subiculum [23]. These anterior-posterior projection characteris-

tics may prove relevant to understanding MTL dysfunction in schizophrenia, as initial data suggest a differential disease related change in anterior MTL.

Medial Temporal Lobe Contributions to Declarative Memory

The anatomic organization of MTL suggests that component regions of the circuit may differentially mediate the acquisition, retention, and recollection of specific classes of stimuli as well as different types of memory representations. Perirhinal and parahippocampal cortices may encode different types of stimuli given that their differential cortical inputs allow for a distinctive pattern of sensory and conceptual convergence and integration. Moreover, the hierarchical organization of the MTL region highlights potential functional segregation between the hippocampus and surrounding MTL cortices. The hippocampus, at the apex of the MTL hierarchy, may combine and extend the representations in MTL cortices, creating conjunctive representations that integrate multiple sources of cortical information, the type of knowledge necessary for declarative memory [1,2,5].

Conjunctive representations separately code the elements of an event, maintaining the compositionality of elemental representations and organizing them in terms of their relations to one another [30]. The elemental nature of such conjunctions allows for reactivation of the extended representation from partial input, a process termed pattern completion [8]. It has been hypothesized that hippocampus, in particular, has the ability to rapidly form conjunctive representations in one trial, whereas MTL cortex requires multiple exposures to abstract the statistical co-occurrences of elements [7,8]. It has been suggested that MTL cortex may be limited in its ability to form conjunctive representations, partially because perirhinal and parahippocampal cortices only have access to specific types of information from neocortical regions. Though controversial [31–35], several convergent findings have supported this hypothesis, including lesion and electrophysiologic data from nonhumans [1,6], and neuropsychological [36–39] and neuroimaging data from humans [40–46].

Given the architecture of the intra-hippocampal subfields, attention has focused on CA3, and its interactions with entorhinal cortex and CA1, in mediating conjunctive processes. A leading hypothesis is that CA3 mechanisms are central to the formation of conjunctive memories that link event elements, as well as to subsequent pattern completion that constitutes retrieval of these representations [8,47,48]. Encoding of conjunctive representations may critically depend on the widespread collateral connections within CA3, comprising a powerful associative learning mechanism that allows for the binding of co-occurring event inputs distributed to multiple CA3 neurons. Supportive evidence comes from studies of CA3-NR1 knockout mice that demonstrate impaired spatial learning on tasks that require the rapid acquisition of conjunctive information [49].

Conjunctive representations may permit recollection at retrieval through pattern completion mechanisms that result in retrieval of an extended representation from partial input. Pattern completion may critically depend on mechanisms in CA3, CA1, and subiculum, and on their interactions. For example, CA3-NR1 knockout mice demonstrate impaired retrieval when cued by a partial set of inputs, as evidenced by a failure to reactivate encoding patterns in CA1 [50]. This finding highlights the putative importance of CA3 in pattern completion, raising interest in the status of CA3 function in populations with expressed declarative memory deficits, such as patients with schizophrenia.

Neuroimaging of Medial Temporal Lobe Function in Declarative Memory

A prerequisite to considering the relation between schizophrenia and dysfunction in MTL substructures is an understanding of the mnemonic contributions of the distinct substructures in the healthy human brain. One source of evidence comes from recent neuroimaging studies using functional magnetic resonance imaging (MRI) that have examined the degree to which the distinct subregions of human hippocampus and the surrounding MTL cortices differentially support particular aspects of declarative memory [40–46]. To date, the majority of such studies have focused on putative functional dissociations between hippocampus and MTL cortex, with initial data demonstrating a correlation between hippocampal mechanisms and the building of conjunctive representations. For example, greater hippocampal activation during encoding correlates with a higher probability of successful recollection (and thus presumably pattern completion) at retrieval, whereas encoding activation in MTL cortices correlates with later successful item recognition regardless of recollection outcome [41,42,45].

Complementing these encoding findings, emerging evidence suggests that MTL cortex demonstrates a particular sensitivity to item familiarity (or conversely item novelty) at retrieval. An initial meta-analysis of four functional MRI studies revealed reductions in activation in anterior MTL cortex during the processing of repeated items compared with novel items, with these reductions failing to track behavioral expressions of source recollection (presumably mediated through pattern completion) [44]. Related findings also suggest the possibility that when items are re-experienced, activation in MTL cortex is reduced relative to the first encounter, and that this reduction can serve as a basis for discriminating between novel and familiar stimuli [6,51]. Consistent with this hypothesis, a recent direct test of this possibility demonstrated that the magnitude of experience-dependent activation reductions in both perirhinal and parahippocampal cortices tracks subjective reports of perceived item familiarity, with the timing of these effects emerging within the first 200 ms

of stimulus processing [52]. Moreover, new data indicate that repetition reductions in perirhinal cortex are sensitive to repetition of conceptual stimulus properties, whereas such reductions in parahippocampal cortex are sensitive to repetition of perceptual stimulus properties [53], a pattern that may stem from the different sources of cortical projections to perirhinal and parahippocampal cortices.

The hypothesized role of the hippocampus in pattern completion at retrieval has also received support from recent functional MRI studies. For example, Eldridge *et al.* [43] observed that increased hippocampal activation during episodic retrieval is associated with conscious recollection of remembering the learning episode. By contrast, in their study, hippocampal activation did not increase for items recognized on the basis of familiarity or for unrecognized items, suggesting a selective role in reactivating conjunctive representations. In related studies, hippocampal activation was associated with trials on which subjects correctly recollected contextual information relative to those trials on which contextual recollection failed [40,54].

Further evidence for the role of the hippocampus in the retrieval of conjunctive (or relational) information comes from studies of transitive inference tasks [55,56]. Transitive inference tasks are designed to test the hypothesis that linked episodes produce representations of a higher-order memory space that store knowledge about the relations between the episodes [1,2]. From the relational perspective, such knowledge allows memory to serve as a basis for inferential judgments that require the flexible bridging across episodes. Transitive inference tasks generally involve an initial learning phase of explicit instruction about associations between items presented in pairs, followed by a critical test asking participants to infer the relationship between items that are related only indirectly through their shared association with one or more intervening items. Two neuroimaging studies examining MTL contributions during such inference tasks demonstrated activation in anterior hippocampus that was uniquely associated with transitive judgments relative to control conditions [57,58]. Importantly, schizophrenic patients demonstrate impaired performance on similar transitive inference tasks [13,15], raising the possibility that such impairments stem from disruption of hippocampal mechanisms that support the formation and retrieval of conjunctive information.

Recent high-resolution functional MRI data suggest that the acquisition and retrieval of conjunctive information may differentially depend on mechanisms in specific hippocampal subregions [10,59]. These newly developed high-resolution functional MRI techniques allow for the differentiation of signal arising from specific subregions within the hippocampus, as well as more precise specification of response localization in MTL cortex. Data emerging from such high-resolution studies suggest differential contributions of dentate gyrus/CA2-CA3 to associative encoding and of subiculum to associative retrieval [10]. Because these techniques allow for investigation of how

substructures of the hippocampus support conjunctive memory processing, a promising direction is their application to questions regarding how the function of specific substructures may be affected in schizophrenia.

Declarative Memory and Medial Temporal Lobe Status in Schizophrenia

Cognitive deficits

Psychosis (hallucinations, delusions, thought disorder) is the prominent, but not the only, symptom set in schizophrenia [60–62]. Two other symptom domains are often described: cognitive deficits (memory, attention, and executive dysfunction) [63,64] and affective changes (negative symptoms) [65,66]. Importantly, it is the cognitive dysfunction of schizophrenia that is associated with poor psychosocial function in the illness [67], thus identifying cognitive improvement as vital for illness recovery.

Within the cognitive domain, deficits in attention, vigilance, and working memory are often accompanied by impairments in declarative memory [64,68–72]. For example, persons with schizophrenia take longer to encode a stimulus than do healthy control subjects, although they can eventually achieve normal levels of memory performance with multiple study exposures [15,73] (Tammimga, Unpublished data). Similarly, the capacity to build associations and abstractions is impaired in individuals with the disease [15,68], including deficits in making transitive inference decisions [13,15]. Moreover, some unaffected first-degree relatives of schizophrenia probands demonstrate many of these same cognitive deficits [67]. Specifically, measures of declarative memory, auditory attention, and abstraction differentiate relatives of schizophrenic probands from healthy control subjects [74]. Whether these cognitive abnormalities are all correlates of a single primary neuropathology or whether they each have their own distinct mechanisms is not yet known. However, given that approaches to the study of MTL-dependent memory are fairly advanced, the possibility of addressing altered hippocampally mediated memory mechanisms in schizophrenia may be particularly timely.

Medial temporal lobe status in schizophrenia

Clues about schizophrenia pathology have emerged from the postmortem literature, with data indicating that the hippocampus, prefrontal cortex, and dorsal thalamus are particularly affected in persons with the illness [75]. Within hippocampus, CA1 is relatively spared, whereas neuropathologic features associated with schizophrenia are concentrated in CA3/4 [11]. Changes in synaptic proteins [12], glutamate receptors [76], glutamate receptor subunit expression [77], and gamma-aminobutyric acid receptors [78] associated with schizophrenia have all been observed in CA3/4. Localization of neuropathology predominantly in CA3/4 in schizophrenia is particularly intriguing given that, as mentioned, deletion of the NR1

subunit of *N*-methyl-D-aspartate (NMDA) receptors in CA3 in genetically manipulated mice (a subunit critical for NMDA-R function) results in a deficit in spatial conjunctive memory in the animals [49,50]. Such a defect is consistent with the behavioral expression of conjunctive memory failures in schizophrenia [15].

Given that CA3 has dense, recurrent excitatory projections that may support the building and reactivation of conjunctive representations [8], disruptions in CA3 function in schizophrenia could lead to impairments in declarative memory tasks that require the use of conjunctive representations. Impaired CA3 function could prevent both the rapid acquisition of conjunctive information and subsequent pattern completion that allows for retrieval of conjunctive information from partial cues, both of which are thought to rely on CA3 [9,49,50] and CA3 interactions with other hippocampal substructures. Dysfunction in CA3 processing may propagate forward to CA1 and backward to entorhinal cortex, leading to extended functional impairments within the MTL memory circuit and beyond. Evidence from *in vivo* imaging in schizophrenic patients provides tentative support for this hypothesis, demonstrating that hippocampal efferent connections to anterior cingulate cortex and prefrontal cortex are functionally disconnected during performance on some cognitive tasks [14]. Thus, some of the broader disturbances in cognitive function associated with schizophrenia, including impaired performance on tasks that focus on abstraction or associative memory processing, may result from this suggested disruption in CA3 processing.

Neuroimaging of Medial Temporal Lobe in Schizophrenia

Structural neuroimaging

In vivo hippocampal volume is reduced bilaterally in schizophrenia, especially in anterior areas [79–82]. This reduction in size is seen as early as the first psychotic episode [83,84]. It has been detected to a lesser degree in nonpsychotic siblings of schizophrenia probands [85] and in persons at risk for schizophrenia [86,87]. Moreover, studies of hippocampal shape have suggested regional abnormalities of contour in individuals with schizophrenia [88] and in nonaffected siblings of schizophrenic probands [85]. Importantly, these regional-shape abnormalities occur predominantly in the head of the hippocampus, implicating the anterior subregion within hippocampus as abnormal [89]. To the extent that shape abnormalities reflect pathology in underlying tissue, these data further support the presence of alteration in hippocampus associated with the illness.

Functional neuroimaging

Neuroimaging studies have begun to characterize alterations in metabolism and functional activity within the MTL region in schizophrenic patients. Initial positron

emission tomography (PET) studies measuring regional cerebral glucose metabolic rates (rCMRglc) during rest demonstrated differences in hippocampal rCMRglc in schizophrenic patients relative to healthy control subjects [90–94]. Some studies revealed decreased hippocampal rCMRglc in schizophrenic patients relative to control subjects [90–92], whereas others observed increased rCMRglc in patients with negative symptoms in addition to those with severe hallucinations and delusions [93,94].

Along similar lines, PET studies using measures of regional cerebral blood flow (rCBF) have demonstrated rCBF increases in MTL in schizophrenic patients [95–98], with rCBF during rest being correlated with clinical symptoms. For example, increased rCBF in left MTL in schizophrenia was associated with more severe psychopathology [95] or with more positive symptoms, such as hallucinations and delusions [98]. Moreover, increased hippocampal activation has been observed when schizophrenic patients experience auditory hallucinations using both PET and functional MRI [99–101]. Together, these studies document abnormal hippocampal function in schizophrenia during periods of rest that is associated with the psychopathology of the disease.

Initial PET studies have also documented alterations in hippocampal activation while schizophrenic patients performed declarative memory tasks. Increases in hippocampal rCBF in schizophrenic patients relative to healthy control subjects were observed during an auditory recognition task [14], though differences in hippocampal activation in schizophrenic patients were not limited to the recognition conditions but were also observed in the rest and control conditions, suggesting a general elevation in hippocampal rCBF in schizophrenia. Atypical hippocampal activation in schizophrenia has also been observed when declarative memory retrieval was elicited by requiring the recall of previously studied words [13,102,103]. Across-group comparisons revealed that hippocampal activation in schizophrenic patients was elevated relative to the healthy control group during both recall and baseline conditions. However, within-group comparisons revealed no difference in hippocampal activation between recall and baseline blocks within the schizophrenic group, whereas a robust difference in hippocampal activation between recall and baseline conditions was observed within the healthy control group. This failure to recruit MTL regions during recall (no differentiation in hippocampal activation between recall and baseline) was accompanied by impaired performance on the memory task in the schizophrenic patients [13,103]. Although important initial observations, these studies lacked sufficient resolution (both spatial and temporal) to generate precise information about the localization of activations within subregions of MTL.

Functional MRI studies, which offer better spatial and temporal resolution than PET, have demonstrated abnormal patterns of MTL activation in schizophrenia during both memory encoding and retrieval. In a block-design functional

MRI study, schizophrenic patients and healthy control subjects performed a picture-encoding task on both novel and familiar stimuli [104]. Despite intact subsequent recognition memory performance for the presented pictures, schizophrenic patients demonstrated abnormal encoding-related activation in the hippocampus and parahippocampal gyrus relative to healthy control subjects. Specifically, whereas healthy subjects demonstrated greater MTL activation for novel relative to repeated stimuli, patients with schizophrenia demonstrated the opposite pattern of response [104]. In a related functional MRI study of novel face encoding, schizophrenic patients showed reduced hippocampal activations relative to healthy control subjects, even though later recognition was comparable across groups [105]. When encoding activation during novel picture learning was sorted by later memory performance [106–108], schizophrenic patients demonstrated different patterns of MTL activation than healthy control subjects, even though recognition performance was equivalent [109].

Investigations of hippocampal activity during memory retrieval have also revealed altered patterns of hippocampal activation in schizophrenia [110,111]. For example, during recognition memory for previously presented words, reduced hippocampal activation was observed in patients relative to healthy control subjects during the evaluation of novel foil items at the time of retrieval [110]. Although both schizophrenic patients and healthy control subjects demonstrated above-baseline hippocampal activation during presentation of old and new items, only in healthy control subjects did hippocampal activation differentiate between old and new items. Strikingly, the schizophrenic patients performed worse on the recognition memory task relative to control subjects due to a high false-alarm rate, suggesting that the failure of hippocampal activation to differentiate new items from those previously experienced underlies the patients' memory deficits. Jessen *et al.* [111] also observed differences in recognition memory performance in schizophrenia that were associated with reduced activation in the left anterior hippocampus during successful encoding and reduced hippocampal activation bilaterally at retrieval relative to healthy control subjects [111].

An electrophysiologic study measuring event-related potentials also observed important differences in brain responses during memory retrieval between schizophrenic patients and healthy control subjects [112]. Using the remember/know procedure, in which subjects are required to judge whether recognition was associated with a recollective experience ("remember") or a feeling of familiarity ("know"), schizophrenic patients had fewer "remember" and more "know" responses than healthy control subjects. In addition, the timing of responses over temporo-parietal sites for "remember" items relative to "new" items was different for schizophrenic patients relative to healthy control subjects, with patients demonstrating a shorter time course of activity. These results are especially intriguing given findings in healthy adults that memory accompanied by con-

scious recollection of contextual details is associated with increased activation in hippocampus [40,43]. The relative lack of “remember” responses in schizophrenia patients may reflect disruption in hippocampal processing, which leads to differences in the timing of neural responses as observed with event-related potentials.

Taken together, functional imaging studies in schizophrenic patients provide evidence for abnormal hippocampal function in the disease that is often associated with impaired declarative memory performance. However, changes in activity in hippocampal regions can appear even when memory performance is apparently intact [104,109]. This variable pattern indicates that although functional imaging in schizophrenia has advanced our understanding of how changes in structure relate to specific changes in memory function, important questions remain. In light of converging evidence from animal and human studies implicating specific MTL subregions in distinct aspects of declarative memory function, the variable imaging outcomes in schizophrenia may reflect the presence of functional abnormalities in specific hippocampal subregions, with other subregions remaining functionally intact. Future studies using recently developed high-resolution functional MRI methods are likely to provide insight into these questions.

Conclusions

Anatomically guided models of MTL function may fruitfully guide future explorations of the neuro- and psychopathology-associated with schizophrenia. The presence of declarative memory impairments and correlated abnormalities in hippocampal function as revealed by functional neuroimaging suggest a clear role for the hippocampus and surrounding MTL structures in the pathology of schizophrenia. Further evidence from structural neuroimaging that the CA3 region of the hippocampus may be particularly affected in the disease suggests that the declarative memory impairments observed in schizophrenia arise from impairments in conjunctive processing, which is hypothesized to rely on the CA3 region and its interactions with other hippocampal regions. High-resolution functional MRI techniques that allow differentiation between hippocampal subfields provide new means to directly investigate disruptions in CA3 function that may be associated with observed structural abnormalities in schizophrenia. The ability to observe and characterize CA3 function, and MTL function more broadly, in schizophrenia promises to advance understanding of how declarative memory in general, and conjunctive processing in particular, are affected in the disease and may provide insight into possible treatment interventions.

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