Plasticity, Hippocampal Place Cells, and Cognitive Maps

Matthew Shapiro, PhD

Memory of even the briefest event can last a lifetime. Thus, learning and memory require neuronal mechanisms that allow rapid, yet persistent, changes to brain circuits. Hippocampal neuropsychology, synaptic and cellular electrophysiology, pharmacology, and molecular genetics converge and begin to reveal these mechanisms. Lesions of the hippocampus profoundly impair memory for recent events in humans and rodents. Circuits within the hippocampus are remarkably plastic, and this plasticity is mediated in part through changes in synaptic strength and revealed by long-term potentiation (LTP) and long-term depression (LTD). N-methyl D-aspartate (NMDA) receptors, a subtype of glutamate receptor, are crucial for inducing these plastic changes, and blocking these receptors reduces plasticity and impairs learning in tasks that require the hippocampus. Molecular genetic alterations that disrupt signaling mechanisms downstream of the NMDA receptor also prevent LTP induction and impair hippocampus-dependent learning. N-methyl D-aspartate receptor mechanisms have also been linked to information coding by hippocampal neurons. Hippocampal cells fire selectively in specific and restricted locations (place fields) as rodents move through open environments. Place fields form within minutes and persist for months. N-methyl D-aspartate receptor antagonists prevent the establishment of stable place fields. The same molecular genetic manipulations that interfere with hippocampal NMDA receptor function, prevent LTP induction, and impair spatial learning also disrupt the formation of stable hippocampal place fields. Finally, learning has been improved in mice with genetically modified NMDA receptors that enhance LTP induction. Thus, hippocampal cells “learn” to encode the salient features of experience through NMDA receptor–dependent synaptic plasticity mechanisms, and this rapid and persistent neuronal encoding is a crucial step toward the formation of long-term memory. Disruption of these plasticity mechanisms may underlie age-related memory deficits.

MEMORY AND AMNESIA

In 1957, Scoville and Milner described a patient whose medial temporal lobes were removed as an experimental treatment for epilepsy. The surgery reduced the patient’s seizures, but also caused severe amnesia. After his surgery, the patient was unable to learn new facts or remember recent events, though both his short-term memory and childhood memories remained intact. Neuropsychological studies of other temporal lobe lesion cases suggested that damage to the hippocampus caused this anterograde amnesia. Research since then focused upon how medial temporal lobe structures, the hippocampus in particular, contribute to memory.

ANIMAL MODELS OF AMNESIA

Memory, in the everyday sense of the word, hinges on remembering events: what happened in a place once upon a time? People
can describe episodes in words, and the accuracy of their memory can be verified. People with amnesia cannot remember recent events. The ability to remember the personal, spatial, and temporal context of events has been called episodic memory, described in detail by Endel Tulving.2

A major challenge to the neuroscience of memory was to establish valid animal models of amnesia in nonverbal species. This limitation of animal behavior forced researchers to define memory in terms of abstract cognitive processes such as information encoding, manipulation, storage, and retrieval, and to translate those ideas into behavioral tests. Rapid progress followed the discovery of dissociations among multiple memory systems during the 1970s and 1980s. We know now that several special-purpose memory systems process and store different types of information. O'Keefe and Nadel's The Hippocampus as a Cognitive Map3 helped establish the idea of multiple memory systems by emphasizing that animals could represent the same physical stimuli differently using different neuronal systems. They showed that locations are defined not by single items, but rather by the unique set of spatial relationships among common items, so that the perspective from one place distinguishes that location from any other. Hippocampal lesions impair many tasks that require memory for spatial relationships. In contrast, rats learn to approach or avoid simple stimuli (eg, a light) with brain circuits that require the dorsal striatum but not the hippocampus.4 This dissociation has been shown in the radial maze devised by David Olton and colleagues (Figure 1C).5 To test hippocampus-independent memory, hungry rats are trained to enter arms that are marked by a light to obtain food and to avoid unlit arms that contain no food. In this cue approach task, lesions of the neostriatum impair learning, but rats with hippocampal damage learn faster than normal ones. To test hippocampus-dependent spatial memory, a piece of food is placed at the end of each arm at the start of a trial. To obtain the food efficiently, the rat must enter each arm once and only once each day. Normal rats remember visited arms for 12 hours or more with no decrement in performance, so this ability is not simply one of short-term memory. As long as the animal is prevented from learning a stereotyped response pattern (eg, always turning left), hippocampal lesions made by any method, before or after training, permanently impair performance. This and other dissociations among different memory systems show that motivation, perception, motor ability, and other variables that are common among the tasks cannot explain the effects of hippocampal lesions. Rather, the dissociations show that the effects of hippocampal lesions are selective for memory—in this case, memory for recently entered locations.

As reviewed by Eichenbaum and colleagues,7 many tasks that require memory for nonspatial relationships are also impaired by hippocampal lesions. Thus, spatial memory is an important and useful example of a more general memory capacity provided by the hippocampus across species. The refinement of animal models allows specific aspects of memory to be tested, which in turn requires specific neural circuitry and provides a crucial step toward the evaluation of memory mechanisms at neuronal, synaptic, and molecular levels of analysis.

SYNAPTIC PLASTICITY IN HIPPOCAMPAL CIRCUITS

Learning and memory require persistent changes in neuronal circuits. These changes, according to Donald Hebb's hypothesis,8 occur when the connections between coactive cells change and thereby store a record of an event. Indeed, hippocampal circuits support rapidly induced and persistent synaptic plasticity (Figure 1A). Bliss et al9,10 discovered that high-frequency electrical stimulation of hippocampal circuits produced an enhancement of synaptic responses that lasted for hours in vitro and days to weeks in vivo. They named this enduring response long-term potentiation (LTP).

The discovery of LTP and its inverse, long-term depression (LTD), in a brain structure associated with memory and amnesia suggested a biological implementation of Hebbian synapses. The link between LTP and learning could not be tested, however, unless and until LTP could be manipulated independently from normal synaptic transmission. Fortunately for the neuroscience of memory, the mechanisms of LTP induction can be separated from normal synaptic transmission, at least in the hippocampus. (The induction, maintenance, and expression of LTP are defined operationally and refer to the moment when evoked potentials are measured.) In the hippocampus, LTP induction requires the N-methyl-D-aspartate (NMDA) type of glutamate receptor and is blocked by NMDA receptor antagonists, whereas LTP expression and normal neurotransmission are conveyed by non-NMDA (AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid]) glutamate receptors.11 The NMDA receptor is required to induce LTP because Ca2+ influx through the NMDA receptor channel is the first signal that ultimately changes synaptic strength. The NMDA-associated Ca2+ channel is gated by both voltage and ligand. To open the channel, the postsynaptic membrane must be strongly depolarized at the same time that glutamate occupies the receptor site. Thus, the NMDA receptor detects presynaptic and postsynaptic coactivation, much as predicted by Hebb.8 If presynaptic and postsynaptic elements are coactive and calcium influx is sufficient, then the strength of the synapse increases. Note that the NMDA receptor is only crucial for this induction step and that normal synaptic transmission, including that through potentiated synapses, does not require NMDA receptors. Thus, while blocking NMDA receptors prevents the induction of LTP, it does not prevent the expression of LTP.

SPATIAL LEARNING AND ENDURING RECENT MEMORY REQUIRE NMDA RECEPTOR–DEPENDENT SYNAPTIC PLASTICITY

Psychopharmacology

Research on LTP accelerated after Richard Morris and colleagues12...
onstrated that blocking NMDA receptors impaired learning in tasks that require the hippocampus. Long-term potentiation induction in the dentate gyrus and spatial learning in the water maze were impaired by the NMDA receptor antagonist amino-phosphonovalerate (APV). In contrast, neither the expression of previous learning nor visual discrimination learning in the same apparatus was impaired by the drug. Direct infusion of APV into the hippocampus produced the same pattern of effects. These findings established a testable link between a biophysical mechanism and memory formation in the mammalian brain.

N-methyl D-aspartate receptor antagonists also impair spatial learning, but not performance, in the radial maze. Doses that reduce potentiation in hippocampal circuits prevent rats from learning the task.
establishment of new memories. Unfamiliar room. The rats given saline performed well in the new room within a few trials. The rats given the NMDA receptor antagonist, however, performed poorly.

The experiment, primed burst potentiation was used to induce a short-lived form of plasticity. C, NMDA receptor antagonists prevent normal spatial learning in the radial maze. The figure on the left depicts a rat in an 8-arm radial maze surrounded by distal cues. The task for the rat is to enter each arm once to obtain food placed at the end of each arm at the start of the daily trial. Probe tests have shown that rats remember which arms they have visited on the basis of the distal cues. Hippocampal synaptic potentiation is shown by recording electrodes placed in the radial maze. The figure on the right shows the complete block of synaptic potentiation in area CA1 produced by the NMDA receptor antagonist CPP (10 mg/kg). In this experiment, primed burst potentiation was used to induce a short-lived form of plasticity. C, NMDA receptor antagonists prevent normal spatial learning in the radial maze. The figure on the left depicts a rat in an 8-arm radial maze surrounded by distal cues. The task for the rat is to enter each arm once to obtain food placed at the end of each arm at the start of the daily trial. Probe tests have shown that rats remember which arms they have visited on the basis of the distal cues. Hippocampal lesions made by any method permanently impair performance on this task. The graph on the right illustrates the effects of NMDA receptor antagonists on radial maze performance. The vertical axis shows repeated arm entries, while the horizontal axis shows blocks of trials. In this experiment, 2 groups of rats were trained under normal conditions to perform the radial maze task. Thus, the NMDA receptor antagonist CPP ((+/−)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) or aminophosphonovalerate (APV) completely prevents LTP.

The same doses do not impair memory performance, as long as rats are first trained and then tested in the same, familiar environment. The drugs therefore do not alter motivation, perception, or sensorimotor function enough to disrupt memory performance. Furthermore, the same animal that performs the radial maze task well when drugged and tested in a familiar room performs poorly when tested in an unfamiliar room. The simplest interpretation of these results is that the drug impairs learning about the particulars of an environment. This view is bolstered by the fact that NMDA receptor antagonists also prevent the establishment of new neuronal representations in the hippocampus.

Molecular Genetics

The effects of NMDA receptor antagonists on learning in rodents have been confirmed by molecular genetics experiments in mice. Two classes of mutations show that NMDA receptor activation is required for synaptic plasticity mechanisms in the hippocampus that mediate hippocampus-dependent learning: localized NMDA receptor elimination and disruption of signaling pathways downstream of the NMDA receptor (Figure 2A).

Joe Tsien and colleagues,14 then in Susumu Tonegawa’s laboratory at the Massachusetts Institute of Technology, created mice that lost their NMDA receptors selectively in the cornu ammonis 1 (CA1) layer 3 weeks after birth. Because the receptor elimination was both region selective and postnatal, the mutation was less likely to disrupt either normal development or widespread brain circuits. The mice without CA1 NMDA receptors had normal neurotransmission but no LTP in CA1 and were severely impaired in the hippocampus-dependent, spatial version of the Morris water maze (a task in which a platform that can be found only by learning and remembering its spatial location is hidden underwater). In contrast, the mice learned to escape the water onto a visible platform, demonstrating that motivation, sensation, perception, motor function, and extrahippocampal learning systems were intact. More recently, a mutation was produced in which CA1 NMDA receptors can be deleted and reinserted through the use of tetracycline (a so-called inducible/reversible mutation). These mice learn the spatial version of the water maze task only when CA1 NMDA receptors are available and become impaired after the receptors are eliminated. This class of experiments provides perhaps the strongest evidence that links NMDA receptor function, synaptic plasticity, and hippocampus-dependent learning ability.

Similar results were reported by Alcino Silva and others15,16 in mice with mutations that altered intracellular signaling downstream of the NMDA receptor. Mice without or with mutated forebrain calcium-calmodulin–dependent kinase II (CaMKII) have abnormal hippocampal LTP and impaired hippocampus-dependent learning. CaMKII is activated by calcium influx through the NMDA channel and is necessary for LTP induction. Other mutations prevent the induction or persistence of LTP by impairing other signaling pathways downstream of the NMDA receptor, and each mutation prevents new spatial learning in the water maze. These include mutations to CREB (cyclic adenosine monophosphate–re-
responsive element binding protein) and protein kinases C and A. Mice with these mutations are impaired in several tasks that require the hippocampus, such as contextual fear conditioning and social transmission of food preferences. Again, cue approach learning that is unimpaired by hippocampal damage is not impaired by either NMDA receptor antagonists or mutations to LTP induction pathways.

Mutations in CREB and protein kinase A (PKA) pathways reduce the persistence, rather than the induction of LTP and provide especially powerful evidence of the importance of NMDA-dependent plasticity mechanisms for learning (Figure 2A). Ted Abel and others, then in Eric Kandel's laboratory, and Alcino Silva and others showed that mice with such mutations learn normally and perform well when tested shortly after train-
Figure 2. Hippocampal place fields, learning, and synaptic plasticity. A, Cornu ammonis 1 (CA1) and CA3 pyramidal neurons have distinct complex-spike action potentials whether recorded intracellularly or extracellularly. These signature complex-spike cells occasionally fire in bursts of 2 to 7 action potentials with decreasing amplitude. Advances in microelectrode recording methods allow these cells to be discriminated with high accuracy by the unique pattern of waveforms across 2 (stereotrode) or 4 (tetrode) adjacent electrode wires. Place cells: When rats explore open environments, eg, a 4-arm maze surrounded by stimuli, hippocampal pyramidal cells fire in restricted locations called place fields, shown in a computer-generated place field “map” (right). A computer combines the action potentials fired by a single hippocampal cell with the animal’s location, detected by an overhead video camera; each small square represents an area on the radial maze visited repeatedly by the rat during a 10-minute recording period. The small squares in the map show locations entered by the rat, and filled squares show that significantly elevated firing rates occurred in a restricted region (southwest maze arm). The cells respond to relationships among distal cues, in particular, to the distance between the rat and a relatively small subset of the available stimuli, S-comm indicates Schaffer collaterals/commissural inputs; mf, mossy fivers; DG, dentate gyrus; PP, perforant path; and EC, entorhinal cortex. B, Place fields form rapidly and persist. The figure shows the spatial distribution of neuronal activity recorded from a pyramidal neuron in the CA1 region of a rat during the first 2 days it explored a new environment. The environment was an enclosed square arena. Locations entered by the rat are shown by small squares, the firing rate is shown by line density, and the waveforms show stereotrode recordings taken at the beginning of each day’s recording session. The left-hand panel shows the firing during the rat’s first 5 minutes of exploration in the recording chamber; the right-hand panel shows the first 5 minutes of firing 24 hours later. The scattered firing that appears during the first day begins to focus by the end of the first recording session, and the region with the highest firing, the middle right-hand wall, persists through the second day. The visual impression of focusing is verified by statistical measures including spatial information that measure the likelihood that the rat occupied a pixel given that the cell fired (from left to right, 0.47, 0.85, and 1.3 bits per pixel). C, N-methyl D-aspartate (NMDA) receptor antagonists do not prevent normal cell field activation. Normal rats have place-stable fields. In a familiar environment, the same fields can be recorded for months. When normal rats are placed in a novel environment, however, the firing maps change rapidly to form new place field maps. Within 30 minutes or less, these new fields become stable. Place fields were recorded in rats as they explored a square, enclosed, and highly familiar recording chamber. Place fields recorded in the chamber were stable and unchanged (a and b) in that environment when the rats were given doses of an NMDA receptor antagonist (NPC-17742 or CPP [(+/-)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid]) that had prevented induction of long-term potentiation (LTP) in previous experiments. Thus, the drugs that blocked LTP induction and learning but neither LTP expression nor memory retrieval did not impair the sensory, motor, motivational, or other information-processing functions that are required for normal place field activation. Establishing stable place fields in unfamiliar environments requires NMDA receptor function. A cylinder introduced into the recording chamber defined a new and unfamiliar environment for the animals and produced new spatial firing patterns. This normal remapping was not prevented by NMDA receptor antagonists (c, day 1). The drugs prevented the establishment of stable place fields; the next day, the same cell was remapped again and had yet another field. Thus, blocking NMDA receptors prevents the establishment of stable place fields, but does not prevent either the activation of previously established stable fields or the formation of temporary fields (Kentro et al.14). CCD indicates charge-coupled device.

Better Learning Through Molecular Genetics?

If the NMDA receptor is crucial for learning and memory, can its function be altered to improve memory? In a fascinating counterpart to these molecular genetic “lesions,” Ya-Ping Tang and colleagues19 in Joe Tsien’s laboratory at Princeton University describe improved learning and memory in mice engineered to overexpress the NR2B subunit of the NMDA receptor. N-methyl D-aspartate receptors are complexes that contain various combinations of NR1 and NR2 subunits. The NR2 subunit regulates the duration of Ca2+ influx through the NMDA ion channel. Hippocampal cells taken from mice that overexpressed the NR2B subunit had prolonged NMDA currents and more easily induced LTP than normal cells. The mutant mice learned the Morris water maze, contextual fear conditioning, and novel object discrimination more rapidly than normal, wild-type mice. Most impressively, the NR2B mice showed more rapid extinction to the fear conditioning than wild-type mice, implying that the enhanced learning was flexible. The NR2B mice, therefore, had both enhanced synaptic plasticity in the hippocampus and more rapid learning than normal mice. These results provide important evidence that helps to link NMDA receptor function, synaptic plasticity, and hippocampus-dependent learning. The results also raise many questions: Can learning-enhanced mice show the same behavioral flexibility as normal mice, or are they “sticky,” ie, learning rapidly but then perseverating? Do they have supernormal storage capacity, or do they just “fill up” their memory space more quickly? Does the enhanced memory improve problem solving beyond memory itself? The creation of these and other engineered species promises to illuminate the neuroscience of memory more brightly than ever before.

Hippocampal Neuronal Activity and Behavior

The activity of hippocampal neurons correlates with the salient features of virtually every situation in which hippocampal cells are recorded. Hippocampal neurons respond robustly and selectively in relation to either the discriminative stimuli or the behavioral responses that constitute task performance or both in every experimental situation in which an animal behaves.7 The wide-ranging correlates of cell firing, together with the effects of hippocampal lesions, are consistent with an episodic memory function of the hippocampus. One of the most striking correlates of hippocampal neuronal activity is the place field—the location-specific firing of single hippocampal cells observed as rodents explore open environments. These spatial correlates have been studied extensively, are closely linked with spatial memory, and provide crucial insights into hippocampal neurobiology.

HIPPOCAMPAL PLACE FIELDS

Discovery

In 1971, O’Keefe and Dostrovsky10 discovered that, as a rodent moves about a large environment, the firing rate of hippocampal cells correlates with the animal’s location (Figure 1A). This spatially selective firing pattern led O’Keefe and Dostrovsky to call such neurons place cells and to suggest that place cells encoded a map-like representation of a rat’s location in its environment.1 Most hippocampal cells are almost silent in most places, firing less than 1 spike per second, while in other areas, the firing rate can exceed 100 Hz. A typical cell fires predominantly in one contiguous region; this is the cell’s place field (Figure 1A). Recent experi-
ments by Matthew Wilson and Bruce McNaughton have shown that as few as 60 simultaneously recorded cells can predict a rat's location to within 1 cm.

**Recording and Analytic Methods**

Modern place field studies typically use a video camera to record the location of the animal and a computer to store action potentials along with the camera output. Together, these data allow location-related firing to be assessed rapidly as time-averaged “firing maps” that show the mean firing rate (spikes per second) in each X-Y coordinate (pixel) of a spatial array. These firing maps usually depict place fields from an overhead view of an environment or maze, with color, line density, or a 3-dimensional perspective showing cell-firing rates. The visual impression of place field maps can be quantified. Place field borders can be defined as contiguous regions of pixels with firing rates that exceed a predetermined threshold (eg, 3 SEs above the mean firing rate). These “in-field” regions can then be measured for area, “volume” (the sum of pixel rates within an area), and other spatial statistics. To quantify the spatial signal without place field thresholding, which is somewhat arbitrary, spatial coherence (spatial autocorrelation) or information content (in bits per spike) can also be calculated from the firing maps. To quantify the spatial stability of firing over time, the correlation between place field maps is calculated. Stable place fields will produce similar firing maps with high spatial correlations.

**Coding Properties**

Quantitative methods have allowed detailed explorations of hippocampal place field properties. Within any one environment, place fields are consistent from day to day, with the correlation among place field maps recorded on consecutive days typically exceeding 0.7. The location of a place field in one environment, however, does not predict either the existence or location of a place field in any other environment. About 30% of hippocampal pyramidal cells have place fields in any one environment; the rest are silent. Anatomically adjacent cells in the hippocampus do have correlated firing fields, but they do not consistently overlap, nor do they form a spatiotopic map in the way adjacent neurons in the primary visual cortex respond to stimuli in adjacent retinal locations. Rather, neighboring hippocampal cells can fire in widely different places, and anatomically distant cells can fire in identical locations in the same environment. Together, the firing properties suggest that locations are represented by a distributed population code: Each location in an environment is indicated by an anatomically distributed pattern of activity of many hippocampal cells, and each cell contributes to the encoding of many places. Recent experiments have shown that, in open environments, place cells fire as a function of the distance between the animal and a subset of available cues.

**How Do Place Fields Form?**

Place fields form within minutes when a rat first explores a new environment, and the same fields persist for months for familiar places (Figure 2B). In new and unfamiliar environments, place fields form and stabilize quickly. Initially, the cells fire in an unfocused or unstable pattern. After about 5 to 30 minutes, the place fields are stable and focused, and they remain consistent for as long as they are recorded. In familiar, unchanged environments, hippocampal neurons have been shown to have the same place fields for months.

**Synaptic Plasticity and Place Fields**

**Pharmacology.** The rapid formation of persistent place fields requires NMDA receptors. The NMDA receptor antagonist CPP (cis-3-((2-carboxypiperazin-4-yl)-propyl)phosphonic acid), 10 mg/kg, blocks LTP induction in the CA1 region of behaving rats. The same dose impairs spatial learning and long-term spatial working memory in the radial maze, and prevents the formation of stable place fields in new and unfamiliar environments (Figure 2B). In contrast, this drug dose does not prevent LTP expression, short-term working memory in the radial maze, or the activation of previously established place fields in familiar environments. Thus, NMDA receptor−dependent synaptic plasticity is necessary for establishing stable neuronal representations.

**Molecular Genetics.** As described above, mutations in the NMDA receptor or enzymes downstream of the receptor channel cause reduced LTP in CA1 and poor spatial learning. The same mutations produce noisy and unstable place fields. The mutations include region-selective NMDA receptor knockouts, altered CaMKII (CaMKII-Asp286, αCaMKII T286A), CREB (CREB αΔ2), and PKA (PKA RAB). Thomas McHugh et al in Matthew Wilson’s laboratory showed that mice with NMDA receptors “knocked out” only in area CA1 (no LTP in CA1 and impaired spatial learning) had abnormally large place fields compared with wild-type littermates. The enlarged fields are reportedly caused by instability within a place field that may be established by normal plasticity in regions upstream from CA1, including CA3 and the dentate gyrus. Alex Rotenberg et al in Bob Muller’s laboratory and Yoon Cho et al in Howard Eichenbaum’s laboratory showed that, unlike wild-type mice, those with CaMKII or CREB mutations have place fields that change from one recording session to the next, sometimes within minutes, in the same environment. PKA mutations alter the persistence, not the induction, of LTP, so that normal LTP returns to baseline within a few hours, even after strong induction. Mice with protein kinase A mutations also have transient memory in hippocampus-dependent tasks (eg, contextual fear conditioning) and place cells that are stable within a day but unstable across days. Thus, synaptic plasticity is necessary for establishing stable neuronal representations in the hippocampus. The clear inference is that these representations, in turn, are required for enduring spatial memory.

**RELEVANCE TO THE PRACTICE OF NEUROLOGY**

The hippocampal contribution to memory provides a direct link between the analysis of memory in ex-
Hippocampal place fields in these aged rats are both less sensitive to environmental changes and more unstable in unchanging environments. Indeed, Carol Barnes et al.26 showed that old, memory-impaired rats had place fields that were as unstable as those of young rats given NMDA receptor antagonists. In efforts to directly model the causes of Alzheimer disease, transgenic mice have been designed either to overexpress β-amyloid or presenilins or to produce abnormal β-amyloid sequences. Some strains of these mutant mice also have impaired memory, attenuated LTP, and normal LTD. The clear prediction is that these mice will have transient place fields and that the place field instability will correlate with memory impairments.

Accepted for publication November 10, 2000.

Corresponding author and reprints: Matthew Shapiro, PhD, Kastor Neurobiology of Aging Center, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1639, New York, NY 10029-6574 (e-mail: matthew.shapiro@mssm.edu).

REFERENCES

12. Morris RG, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-