A role for NMDA-receptor channels in working memory

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The NMDA class of glutamate receptors has a critical role in the induction of long-term potentiation (LTP), a synaptic modification that may encode some forms of long-term memory. However, NMDA-receptor antagonists disrupt a variety of mental processes[1–6] that are not dependent on long-term memory. For example, they interfere with working memory[1,6], a short-lasting form of memory that is maintained by neuronal activity[7] rather than by synaptic modification. This suggests that there are unknown functions of the NMDA-receptor channel. One hint is that in addition to producing the calcium entry important for LTP induction, NMDA-receptor channels produce voltage-dependent excitatory postsynaptic potentials (EPSPs)[8]. Here, we use a network model to show that such NMDA-receptor-mediated EPSPs could be critical in maintaining working memory. These results provide a mechanistic framework useful in understanding dopamine-NMDA interactions in working memory and the disruption of working memory in schizophrenia.

Working memory is stored by the maintained firing of a memory-specific subset of neurons in networks of the prefrontal cortex[7]. Firing is thought to be maintained by a reverberatory process[9,10], in which active neurons selectively excite each other through recurrent connections. Previous models assumed that this selectivity is due to modifications of synaptic strength during earlier learning experiences, but did not address the question of how novel items could be stored in working memory. For novel items, the storage mechanism cannot depend on pre-existing synaptic selectivity, and LTP is too slow in onset to produce it[11]. Here we show that the voltage dependence of NMDA-receptor-mediated EPSPs can produce the selective excitation that is needed to maintain novel items in working memory.

Figure 1a shows the circuit we analyzed. The pyramidal cells are uniformly interconnected by recurrent excitatory synapses having equal synaptic strengths. When a memory item is to be stored, a subset of these cells is excited by a brief informational input from an external network. To maintain this item (the spatial pattern of the subset) in working memory, these 'active cells' must continue to fire after the external input ceases. Moreover, excitation should not spread to 'inactive' pyramidal cells that did not receive external input. Our main argument is this: if transmission at recurrent synapses is mediated primarily by NMDA-receptor channels, there

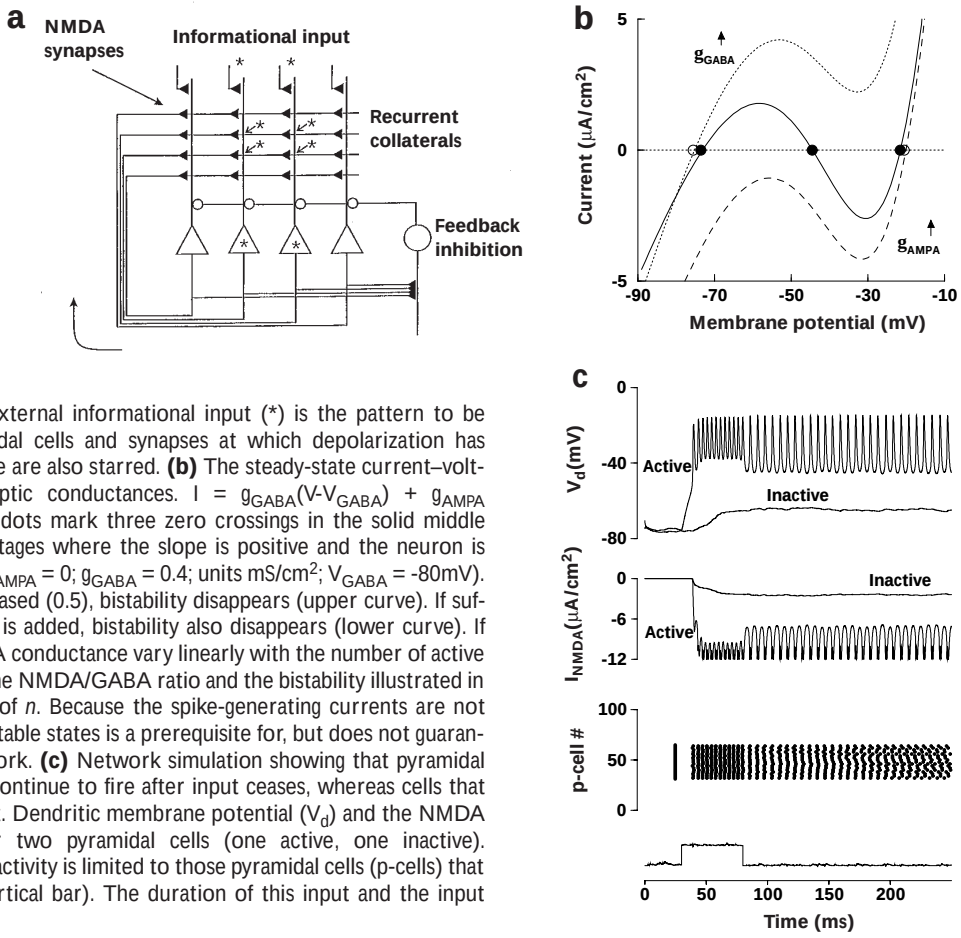

Fig. 1. Maintenance of working memory by NMDA-receptor-mediated synaptic transmission at recurrent synapses. **(a)** Organization of the network used to analyze working memory. Four pyramidal cells (triangles) and one interneuron are shown. The recurrent excitatory connections are all-to-all and uniform in strength. Feedback inhibition is mediated by a group of identically connected interneurons (one shown). The spatial pattern of external informational input (*) is the pattern to be remembered. The active pyramidal cells and synapses at which depolarization has increased the NMDA conductance are also starred. **(b)** The steady-state current–voltage curve for a neuron's synaptic conductances. $I = g_{GABA}(V-V_{GABA}) + g_{AMPA}V + g_{NMDA}V/(1+0.15e^{-0.08V})$. Solid dots mark three zero crossings in the solid middle curve; two of these occur at voltages where the slope is positive and the neuron is therefore bistable ($g_{NMDA} = 2.0$; $g_{AMPA} = 0$; $g_{GABA} = 0.4$; units mS/cm^2; $V_{GABA} = -80$mV). If the GABA conductance is increased (0.5), bistability disappears (upper curve). If sufficient AMPA conductance (0.05) is added, bistability also disappears (lower curve). If feedback inhibition and the NMDA conductance vary linearly with the number of active cells (n), and $g_{GABA} >> g_{leak}$, then the NMDA/GABA ratio and the bistability illustrated in the solid curve are independent of n. Because the spike-generating currents are not included, the occurrence of two stable states is a prerequisite for, but does not guarantee, bistability of the actual network. **(c)** Network simulation showing that pyramidal cells that receive external input continue to fire after input ceases, whereas cells that do not receive input remain silent. Dendritic membrane potential (V_d) and the NMDA current (I_{NMDA}) are shown for two pyramidal cells (one active, one inactive). Rastergram (bottom) shows that activity is limited to those pyramidal cells (p-cells) that received external input (thick vertical bar). The duration of this input and the input noise are shown in bottom trace.

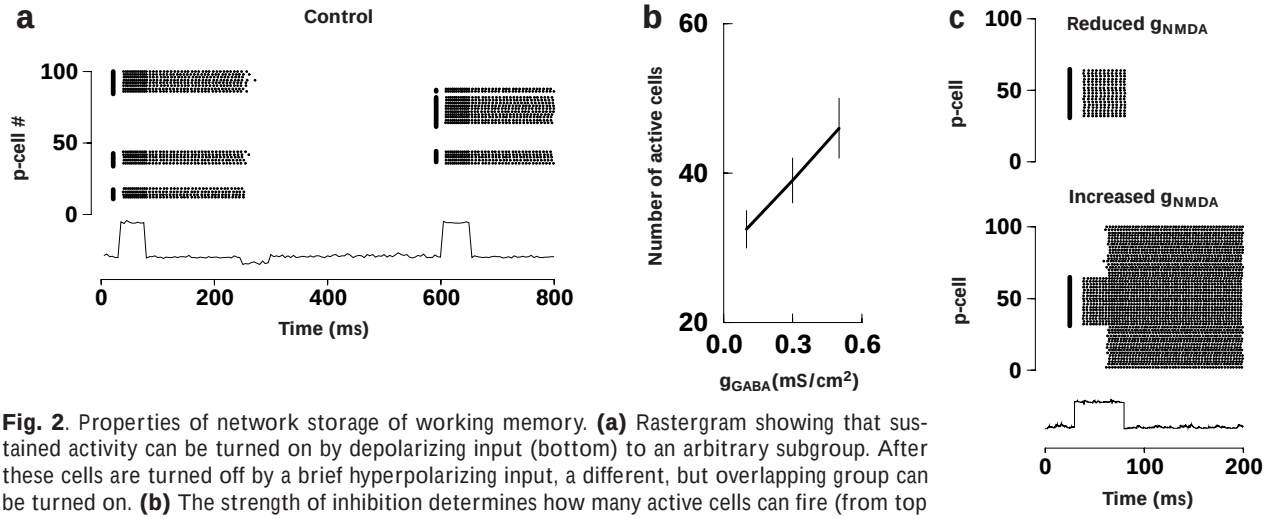

Fig. 2. Properties of network storage of working memory. **(a)** Rastergram showing that sustained activity can be turned on by depolarizing input (bottom) to an arbitrary subgroup. After these cells are turned off by a brief hyperpolarizing input, a different, but overlapping group can be turned on. **(b)** The strength of inhibition determines how many active cells can fire (from top to bottom of vertical bar) in networks that satisfy the conditions for information storage (see part (c)). **(c)** Rastergram shows that if the NMDA-receptor conductance is decreased (33%), there is no sustained activity in pyramidal cells (top); if it is increased (66%) activity spreads to all neurons. It is the intermediate range used in (a) that is useful for information storage because activity is maintained and restricted to the subset of cells that received external input.

will be functionally selective connections between active cells. This is because the voltage-dependence of NMDA-receptor channels makes transmission conditional; transmission requires not only the binding of glutamate, but also substantial postsynaptic depolarization. Thus, when glutamate is released by an active cell onto another active cell, the pre-existing postsynaptic depolarization allows the NMDA-receptor channels to open. The resulting inward current prevents the normal repolarization process and thereby sustains the firing of these cells. In contrast, when glutamate is released by an active cell onto an inactive cell, NMDA-receptor channels will not open significantly because the postsynaptic voltage is near resting potential, a voltage range in which NMDA-receptor channels are almost completely blocked. The small NMDA-receptor current that does occur in these cells will be counteracted by global GABAergic feedback inhibition (Fig. 1a), and inactive cells will thus remain inactive.

The potential for any pyramidal cell to be either active or inactive is a form of bistability. If present, this bistability should be demonstrable in the steady-state current–voltage curve, which is the sum of the NMDA-receptor and GABA-receptor currents as a function of voltage. Under appropriate conditions, bistability is present, because there are two voltages at which there is zero current and positive slope (Fig. 1b). This bistability disappears if the GABA/NMDA conductance ratio is made too high.

To examine the memory storage capability of a network of such neurons (Fig. 1a), we simulated network dynamics using 100 two-compartment pyramidal cells and 20 single-compartment inhibitory neurons. We considered the simplest case, in which the only nonsynaptic conductances were somatic conductances that produce spikes. Maintained activity occurred in the subset of cells that were excited by a brief external input representing the memory (Fig. 1c). The NMDA-receptor current that maintains activity (middle trace) is larger in active cells than inactive cells.. The network allows flexible switching between arbitrary groups representing different memories (Fig. 2a). Selective, maintained firing of the group requires that group size (Fig. 2b) and the ratio of the NMDA to GABA conductance (Fig. 2c) be within a limited range. We conclude that NMDA-receptor-mediated, voltage-dependent transmission allows a network to maintain the activity of novel memories and to do so without the need for synaptic modification.

Our model provides a mechanistic framework for understanding the role of NMDA-receptor channels in working memory.

The network model

The network model consists of N_p pyramidal cells and N_i interneurons. The pyramidal neuron model has two compartments, representing the passive dendrite and the active soma (plus axonal initial segment)[19]. The somatic (V_s) and dendritic (V_d) potentials obey the following current-balance equations: $C_m dV_s/dt = -I_L - I_{Na} - I_K - g_c/p(V_s - V_d) - I_{syn,i} + I_{ext}$; $C_m dV_d/dt = -I_L - g_c/(1 - p)(V_d - V_s) - I_{syn,e}$, with $C_m = 1\ \mu F/cm^2$, $p = 0.5$ and $g_c = 0.5$ mS/cm^2. The leak current $I_L = g_L(V - V_L)$, while the voltage-dependent currents are described by the Hodgkin-Huxley formalism. Thus, a gating variable x satisfies a first-order kinetics, $dx/dt = \Phi_x(\alpha_x(V)(1 - x) - \beta_x(V)x)$. The sodium current $I_{Na} = g_{Na}m^3h(V - V_{Na})$, with $\alpha_m = -0.1(V + 32)/(\exp(-0.1(V + 32)) - 1)$, $\beta_m = 4\exp(-(V + 57)/18)$; $\alpha_h = 0.07\exp(-(V + 48)/20)$, and $\beta_h = 1/(\exp(-0.1(V + 18)) + 1)$. The delayed rectifier $I_K = g_K n^4(V - V_K)$, with $\alpha_n = -0.01(V + 34)/(\exp(-0.1(V + 34))-1)$, and $\beta_n = 0.125\exp(-(V + 44)/80)$. The temperature factor $\Phi_m = \Phi_h = 2.5$, $\Phi_n = 5$. Other values are: $g_L = 0.1$, $g_{Na} = 45$, $g_K = 18$ (in mS/cm^2); $V_L = -80$, $V_{Na} = +55$, $V_K = -80$ (in mV). The excitatory synaptic currents $I_{syn,e} = I_{AMPA} + I_{NMDA}$ are located in the dendrite, and the gating kinetics are similar as in Wang et al.[19]. $I_{AMPA} = (g_{AMPA}/N_p)\sum_i s_i(V - V_{syn})$, where the sum is over all pyramidal cells in the network, the conductance is normalized by N_p and $V_{syn} = 0$ mV. The synaptic gating variable s obeys $ds/dt = k_f F(V_{pre})(1 - s) - k_r s$, with $F(V_{pre}) = 1/(1 + \exp(-V_{pre}/2.0))$, $k_f = 12$ and $k_r = 1$ (in 1/ms). $I_{NMDA} = (g_{NMDA}/N_p)/(1 + 0.3\{Mg\}\exp(-0.08V))\sum_i s_i(V - V_{syn})$, with $\{Mg\} = 0.5$ mM. Second-order kinetics are used to produce a slow onset and decay with different time constants: $ds/dt = \alpha_s x(1 - s) - \beta_s s$, and $dx/dt = \alpha_x F(V_{pre})(1 - x) - \beta_x x$, with $\alpha_x = 10$, $\beta_x = 0.5$, $\alpha_s = 1$, $\beta_s = 0.01$ (in 1/ms). Each compartment also receives Poisson-like current noise ($g = .005$mS/cm^2/λ = 500Hz)). The fast spiking interneuron model and inhibitory synaptic kinetics are taken from[20]. Inhibitory synapses are located in the pyramidal soma. Unless specified otherwise, the maximum conductances are $g_{NMDA} = 3$ (p-to-p) and 0.3 (p-to-I); $g_{AMPA} = 0.04$ (p-to-p) and 0.01 (p-to-I); $g_{GABA} = 0.15$ (I-to-p) (all in mS/cm^2).

Reducing NMDA-receptor-mediated transmission at recurrent synapses should lead to a decrease in memory-associated firing (Fig. 2c). A direct test of the model would be to determine whether the firing of prefrontal units during a memory task is reduced by local application of NMDA-receptor antagonist. Unpublished results (G.V. Williams and P.S. Goldman-Rakic, personal communication) suggest that this is the case. An important requirement of the NMDA mechanism of working memory is that the contribution of the other types of ionotropic glutamate channels (e.g., AMPA channels) at recurrent synapses be low (Fig. 1b). This is because only the NMDA class of ionotropic glutamate receptors has the required voltage dependence of synaptic transmission. This requirement could be met if AMPA channels were absent or if the NMDA/AMPA ratio was made high by neuromodulation. It may therefore be significant that dopaminergic modulation through D1 receptors, which is required for working memory function[12], enhances NMDA-receptor-mediated transmission while reducing the AMPA-receptor-mediated transmission[13]. Most of the studies of this modulation have been done on striatum, and it will be important to determine whether similar modulation occurs in the prefrontal cortex, the site of working memory.

Because NMDA-receptor antagonists can produce a wide range of schizophrenic symptoms, including deficits in working memory, it has been proposed that schizophrenia is caused by the hypofunction of NMDA-receptor channels[4,14], and there is some evidence that this is due to an endogenous NMDA-receptor antagonist[15]. NMDA-receptor-mediated transmission occurs in various brain regions, and NMDA-receptor hypofunction could thus affect several different types of information storage and processing[4,8,16,17]. Our model provides a mechanistic explanation of why NMDA-receptor hypofunction in the prefrontal cortex could lead to the working memory deficits in schizophrenia.

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