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Dopaminergic modulation of the P50 auditory-evoked potential in a computer model of the CA3 region of the hippocampus: its relationship to sensory gating in schizophrenia

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Abstract. We modeled the neuronal circuits that may underlie a sensory-processing deficit associated with schizophrenia. Schizophrenic patients have small P50 auditory-evoked responses to click stimuli compared to normal subjects. The P50 auditory-evoked response is a positive waveform recorded in the EEG approximately 50 ms after the auditory click stimulus. In addition to relatively small amplitudes, schizophrenic patients do not gate or suppress the P50 auditory-evoked response to the second of two paired-click stimuli spaced 0.5 s apart. Neuropleptic medication, which decreases dopaminergic neuronal transmission, increases the amplitude of the P50 auditory-evoked response but does not improve gating. Normal subjects have large P50 auditory-evoked responses to click stimuli when compared to unmedicated schizophrenic patients, and they gate their response to paired click stimuli or have smaller P50 auditory-evoked response amplitudes to the second of two click stimuli spaced 0.5 s apart. Schizophrenic patients do not gate and have similar response amplitudes to both clicks. We hypothesized that the small amplitudes of unmedicated schizophrenic subjects were due to a state of occlusion whereby excessive background noise in local circuits reduced the ability of cells to respond synchronously to sensory input, thereby reducing the amplitude of the P50 waveform in the EEG. Because the P50 auditory-evoked potential amplitudes increased with neuroleptic medication, which reduces dopaminergic neuronal transmission, we hypothesized a role for dopamine in modulating the signal-to-noise (S/N) in the local circuits responsible for sensory gating. To test the hypothesis that modulation of the S/N ratio reduces sensory gating, we developed a model of the effects of dopaminergic neuronal transmission that modulates the S/N in neuronal circuits. The model uses the biologically relevant computer model of the CA3 region of the hippocampus developed in the companion paper [Moxon et al. (2003) Biol Cybern, this volume]. Modified Hebb cell assemblies represented the response of the network to the click stimulus. The results of our model showed that excessive dopaminergic input impaired the ability of cells to respond synchronously to sensory input, which reduced the amplitudes of the P50 evoked responses.

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1 Introduction

P50 auditory gating, as described in the previous paper, has been used as a measure of abnormal sensory processing in schizophrenic patients. While the pathophysiology of schizophrenia is complex and likely involves dysfunction of several neurotransmitter systems (Carlsson et al. 2001; Sharp et al. 2001), including dopamine, across many different neuronal circuits, in the model presented here we examined a role for dopamine in modulating the amplitude of the P50 auditory-evoked potential in the hippocampus. P50 auditory gating is a measure of the suppression of the amplitude of the P50 auditory-evoked potential during a conditioning-test paradigm. The P50 auditory-evoked potential is a positive waveform recorded in the EEG approximately 50 ms after an auditory click stimulus. Schizophrenic patients do not gate or suppress the response to the second click (test response) relative to the response to the first click (conditioning response). This lack of gating was shown to be modulated by cholinergic mechanisms. However, schizophrenic patients appear to suffer from an additional disorder that reduces the absolute amplitude of the conditioning and test response in addition to the deficit in sensory gating examined in the previous paper. It has been suggested that the amplitude of the P50 evoked potential can be used as a measure of S/N and that the reduced amplitude of the P50 auditory-evoked potential of schizophrenic patients

may be a measure of their reduced ability to filter noise and respond with an appropriate, synchronized response to sensory stimuli.

1.1 Reduced P50 amplitude in patients with schizophrenia

It was not initially obvious that this reduction in absolute amplitude of the conditioning and testing responses was a separate deficit from the lack of sensory gating. Yet further studies involving schizophrenic patients showed that not only were these abnormalities two separate deficits but that there were likely separate mechanisms responsible for each deficit. The P50 auditory gating is modulated by cholinergic mechanisms and reduced in schizophrenic patients as well as approximately half of their first-degree relatives (Adler et al. 1982; Siegel et al. 1984; Waldo et al. 1988) (Fig. 1a). However, there is a distinct difference between the amplitudes of the conditioning and test response (CR and TR) of schizophrenics and the CR and TR of their first-degree relatives. The amplitudes of the CR and the TR in nongating first-degree relatives were both very large, like the amplitude of the large CR of normal subjects. However, the amplitudes of the CR and TR of nonmedicated schizophrenic patients were generally small and often smaller than the amplitude of the TR of normal subjects. When the amplitudes of the CR and the TR of nonmedicated schizophrenic patients were compared to the responses of their nongating relatives, the amplitudes of both of these responses in nonmedicated schizophrenic patients were smaller than either the CR or the TR of the nongating relatives regardless of the degree of gating. Further studies suggested that this decrease in the amplitude of CR and TR in schizophrenic patients when compared to their nongating relatives was modulated by traditional neuroleptic medication including haloperidol (Fig. 1b). Therefore, it was concluded that P50 sensory gating and small amplitudes of the CR and TR were two separate deficits with different underlying mechanisms – one cholinergic (P50 sensory gating described in the previous paper) and the other modulated by catechominergic action (amplitude modulation of the CR and the TR described here).

Traditional neuroleptic medication, such as haloperidol, relieves some of the symptoms of schizophrenia and increases the amplitude of both the CR and TR, even though this medication does not improve sensory gating (Freedman et al. 1983; Baker et al. 1987; Adler et al. 1982, 1990; Nagamoto et al. 1993). When the schizophrenic patients are medicated with haloperidol, the amplitudes of both the CR and TR are increased and are similar to the amplitudes of their nongating relatives. While the mechanism of action of traditional neuroleptic medication is nonspecific, haloperidol has been shown to block the action of both dopamine and norepinephrine at postsynaptic receptors. Therefore, the increase of the P50 auditory-evoked potential amplitude in medicated schizophrenic patients suggests a role for catecholaminergic modulation of the CR and TR amplitude.

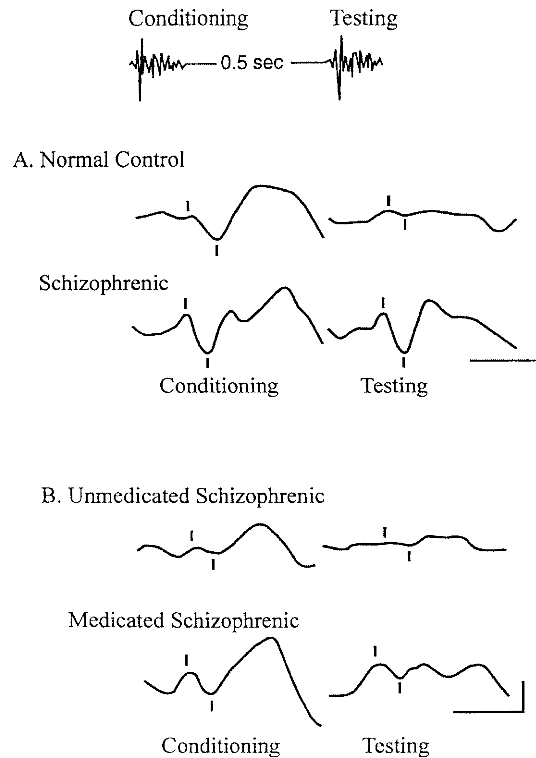

Fig. 1a,b. Recordings of human P50 auditory-evoked potentials of a normal subject and a schizophrenic subject to click stimuli presented in the conditioning-testing paradigm. **a** The normal subject inhibits the response to the test click, while the medicated schizophrenic subject does not. The amplitude of the P50 auditory-evoked potential recorded in response to the conditioning and test stimuli was measured between the two *tick marks* above and below each waveform. The amplitude of the conditioning response for the normal subject was greater than the amplitude of the test response. Gating is measured as the ratio of the test response to the conditioning response (T/C ratio). Small T/C ratios indicate high degree of gating. On average, normal subjects have a T/C ratio of less than 20% while schizophrenic subjects, regardless of medication, have T/C ratios greater than 85% (Adler et al. 1982). The medicated schizophrenic patient has a large amplitude response to both the conditioning and test stimuli, which is similar to the amplitude of the normal subjects' conditioning response. **b** Comparison of the P50 evoked potential recorded from a schizophrenic patient before and during neuroleptic treatment (haloperidol). During medication, overall P50 amplitude increased for the conditioning and test response, but the lack of suppression of the test response persisted. The T/C ratio was 72% before medication and 75% after medication. When the subject is unmedicated, the amplitude of the conditioning and test responses were similar to the test amplitude of the normal subject. These data represent responses to 3 trains of 32 pairs of clicks that were averaged. *Tick marks* below each evoked potential indicate the P50 wave; marks above indicate the point from which amplitude is measured. The P50 evoked response is the positive potential (downward direction is positive) recorded 50 ms after the auditory click stimulus (*top trace on figure*). The auditory stimulus occurs at the beginning of each trace. Horizontal calibration is 50 ms, vertical is 2.5 mV, positive polarity down

1.2 Animal studies of dopamine role in modulating auditory-evoked potential amplitude

To further explore the underlying mechanism of reduced P50 amplitude, we used a rat model of sensory gating. In the rat model, the N40 auditory response is a

negative waveform appearing approximately 40 ms after the stimulus and is analogous to the human P50. In normal rats, when two paired auditory stimuli are presented 0.5 s apart, the rat gates or suppresses the N40 response to the second click stimulus. In our rat model, hyperarousal of the animal, which is a function of increased catecholaminergic neurotransmission, decreased the amplitude of the CR and TR and also reduced gating. Amphetamine and phencyclidine, agents that increase both norepinephrine and dopaminergic neuronal transmission, decreased the amplitude of the N40 evoked response and reduced gating in the rat. This decrease in amplitude and reduction in gating could be reversed by haloperidol, which can block the action of both norepinephrine and dopamine (Adler et al. 1986).

To explore the possibility that the loss of gating and suppression of the amplitudes were due to two independent mechanisms, an agent that selectively depletes norepinephrine, N-(2-chloroethyl-N-ethyl-2-bromobenzylamine) (DSP4) was administered to the animals (Adler et al. 1988). DSP4 attenuated the effect of amphetamine on sensory gating but did not affect the amplitude of the CR or TR. These results suggest that the loss of gating and the reduction in amplitude could be due to two separate mechanisms and that the reduction in amplitude of the P50 auditory-evoked response was due to a dopaminergic mechanism.

1.3 Dopamine's role in modulating the signal-to-noise

We hypothesized that the small amplitudes of the P50 evoked response from nonmedicated schizophrenic patients were due to a decrease in the S/N (Adler et al. 1990). Several investigators have hypothesized a role for dopamine in filtering sensory information (Joseph et al. 1979) or maintaining a high S/N ratio in a neural network (Servan-Schreiber et al. 1990; Cohen and Servan-Schreiber 1992). The decreasing S/N ratio could be due to a simple decrease in the signal, an increase in background noise that obscures the signal, or both. Other studies examining the effects of dopamine on S/N ratio have shown that excessive dopaminergic activity increased the probability of neuronal firing (Bodis-Wollner et al. 1978; Johnson et al. 1983). It is our hypothesis, tested in this paper using a computational model, that if neuronal responsivity is too high, the signal is reduced because hyperresponsive neurons can no longer be activated synchronously by the auditory stimulus. In addition, cells are also responding to many extraneous stimuli or even to random inputs. This increases the background noise. Therefore, hyperresponsiveness increases the background noise and decreases the signal. The evoked response to a stimulus is obscured, which ultimately produces smaller amplitudes of the conditioning and test responses.

1.4 Model hypothesis

In this paper, we used the model developed in the companion paper (Moxon et al. 2003) to study the effects of dopaminergic modulation on the amplitude of the CR and TR of the CA3 network to a simulated auditory click stimulus. The model presented here will test the hypothesis that increased dopaminergic activity is a candidate mechanism for reducing S/N during information recall and ultimately produce smaller amplitudes of the CR and the TR. Furthermore, we will explore the effects of a combined cholinergic and dopaminergic deficit on sensory gating.

As specified in the previous paper, the model simulated the response of the hippocampus to an auditory click stimulus as a modified Hebb cell assembly. The activity of the cells in the assembly produced the auditory-evoked response. When referring to S/N, the synchronous response of the modified Hebb assembly is our definition of signal. Extraneous cell activity not part of the cell assembly represents noise in the system. Several factors could influence the S/N ratio. The decrease in the S/N ratio could be due to a simple decrease in the signal (fewer cells responding synchronously to the response) or to an increase in background noise due to hyperresponsive neuronal activity. We measured the S/N ratio during the response of the network to the simulated click stimulus to quantify the effects of dopamine on S/N in this system. In this way, we were able to examine the hypothesis that excessive, dopaminergic activity increased noise, both in the background and in the lack of synchrony of the response, in the system so that the amplitude of the CR and TR appeared smaller due to a state of occlusion.

Now we would like to address the question of why the signal amplitudes of schizophrenic patients, unlike their nongating relatives, are so small. Evidence from human studies suggests that modulating the absolute amplitude of the P50 auditory-evoked response is a separate mechanism from P50 auditory gating. Evidence from our animal model suggests that dopamine may modulate the amplitude of the P50 auditory-evoked response to a click stimulus independent of modulating P50 auditory gating. We hypothesize that the reduction of the P50 auditory-evoked potential amplitude is due to a decrease in the S/N of the system. This change in S/N is modulated by dopamine. To test the hypothesis that a decreased S/N ratio can reduce the amplitude of the P50 auditory-evoked potential, we simulate the "signal" by a predefined cell assembly and the noise by any activity in the network not defined by the cell assembly (see Representation of signal by cell assembly, Sect. 2.3, below). We added to our model of P50 auditory gating (Moxon et al. 2003) a biologically plausible postsynaptic effect of dopamine on individual cells in the CA3 network (Fig. 2). This action of dopamine in the model modulated the amplitude of the excitatory postsynaptic potentials (EPSPs).

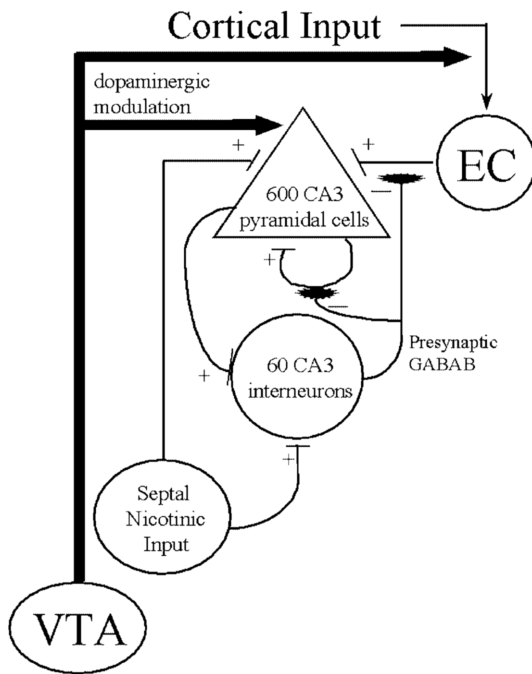

Fig. 2. Schematic representation of the computational model. The model includes 600 individually modeled CA3 pyramidal cells and 60 individually modeled CA3 interneurons. In addition to this local activity, afferents to the network are also simulated. These afferents include simulated cholinergic input from the septum and glutamatergic input from the entorinal cortex and dentate gyrus. The cholinergic input, in addition to activating postsynaptic cholinergic receptors in the model, is also responsible for indirectly activating presynaptic $GABA_B$ receptors through the interneurons. There is also a mechanism to simulate dopamine modulation in the model. Presynatpic $GABA_B$ receptors reduced the amplitude of the EPSPS in a cell. Dopamine modulated the amplitude of EPSPS as a function of membrane potential (*thick black arrows*). VTA – ventral tegmental area. EC – entorhinal cortex

2 Methods

2.1 Phyiological studies of dopamine

Dopamine cells in the ventral tegmental area (VTA) (Chiodo 1988) project to the cortex and limbic system via the mesocortical and mesolimbic dopamine pathways (Deniau et al. 1980; German et al. 1980). This projection is diffuse along slowly conducting fibers, and the firing rate of these cells is low and stable. These characteristics are conducive to modulatory influences. Several mechanisms for dopamine's action in the brain have been postulated. In general D1 and D5 receptor activation enhanced cAMP formation while D2, D3, and D4 tended to decrease cAMP formation (Kebabian et al. 1975; Sokoloff and Schwartz 1995). Berretta et al. (1990) found that D1 agonists produced a hyperpolarization of the resting membrane potential and an increase of the after hyperpolarization amplitude and duration, while a D2 agonist produced a depolarization of the resting membrane potential and a depression of the after hyperpolarization. Physiological studies of the effects of dopamine showed that it has both an inhibitory and an excitatory postsynaptic effect. Krnjevic (1975) found both an inhibitory and excitatory effect in the striatum and a substantial depressive effect in the neocortex.

Both D1-type and D2-type dopamine receptors were found in the hippocampus (Kohler et al. 1991a,b). Binding was mostly in the stratum lacunosum-moleculare, but the D1 receptors were separate from the D2 receptors. Huang et al. (1992), using immunohistochemical localization, found D1 receptors in all regions of the hippocampus, mainly in stratum oriens and stratum radiatum. However, recent advances in cloning techniques have expanded the number of dopamine receptors to include D3-type, D4-type, and D5-type dopamine receptors. It is likely that all three types are found in the hippocampus on both granule cells and pyramidal cells (Sokoloff and Schwartz 1995).

2.2 Structure of the CA3 hippocampal model network

The computational model consisted of 600 CA3 pyramidal cells and 60 CA3 interneurons (Flach et al. 1986; Moxon et al. 2003). The pyramidal cells provided recurrent excitatory synaptic input to themselves and to the interneurons. The interneurons provided recurrent inhibitory synaptic input to themselves and to the pyramidal cells. In addition, two major inputs to the CA3 network were modeled, cortical and septal. The cortical input simulated input from the entorhinal cortex (EC) and dentate gyrus (DG). Each of these inputs provided excitatory input to both the CA3 pyramidal cells and the interneurons. The septal input was modeled after the activity of cells in the medial septal diagonal band complex (MSDB) recorded in response to the paired-click stimuli. The input consisted of two types, cholinergic and GABAergic. The GABAergic input was presumed to contact both CA3 pyramidal cells and interneurons but was shown during recordings in rats not to be sensory responsive. The cholinergic input was of two types, nicotinic and muscarinic. Both types of synapses were modeled on both the CA3 pyramidal cells and the interneurons.

In our previous paper, P50 auditory gating was shown to occur in the model through two related mechanisms (Moxon et al. 2003). The selective activity of nicotinic cholinergic input from the septum to the hippocampus during the conditioning response enhanced the response to the first or conditioning stimulus by increasing the excitability of the pyramidal cells preferentially to the conditioning stimulus. This same cholinergic activity from the septum to the hippocampus attenuated the response to the second or test stimulus by activating presynaptic GABAergic receptors based on data from animal studies (Nagamoto et al. 1991; Hershman et al. 1995). In the computational model (Moxon et al. 2003), these receptors were indirectly activated by the cholinergic input from the septum to interneurons during the conditioning response. A subpopulation of these interneurons activated presynaptic $GABA_B$ receptors.

2.3 Representation of signal by cell assembly

Cell assemblies were defined in the model by ordered sequences of sets of cells that respond to external stimuli (MacGregor and Gerstein 1991; Moxon et al. 2003). For example, the assembly that responds to the auditory click stimulus is composed of 50 cells. For convenience we labeled the cells in this cell assembly 1–50 and refer to it as the test pattern. When referring to S/N this cell assembly defines the signal. At time $t = 1$, cells 1–10 fire, at time $t = 2$, cells 11–20 fire, etc. Each set of cells, i.e., cells 1–10 or 11–20, is called a link. The test pattern is embedded in the network by enhancing synaptic strengths between cells in consecutive links. This defines a set of sender links and receiver links at any given time. A sender link projected to four sets of receiver links. These four sets of receiver links are the sets of links defined to fire in the four consecutive time steps, the first set at the next time step, the second set two time steps ahead, etc. The magnitude of the synaptic strength between a sender link and a receiver link increases as the time between the sender link and receiver link decreases. If only this one test pattern is embedded in the network, when the network is stimulated with the first two links, the test pattern will be activated and each link in the network will fire in consecutive order. For example, if cells 1–10 are stimulated to fire at $t = 1$ and cells 11–20 are stimulated to fire at $t = 2$, these cells will provide synaptic input to cells 21–30 so that these cells fire at $t - 3$. This activity will project synaptic input to cells 31–40 so that they will fire at $t = 4$, and subsequently cells 41–50 will fire at $t - 5$. If more patterns are embedded in the network, synapses are shared between the patterns. This sharing of synapses between different patterns causes cells to fire that are not part of the pattern being recalled. After more than three patterns are embedded in the network, when one pattern is recalled, other cells not in the current pattern being recalled will be activated due to cross-talk activation from these shared synapses (MacGregor and Gerstein 1991). When we define S/N ratio in this model, noise is defined as any extraneous firing of cells other than those that define the pattern. For the simulations performed in this study, four patterns were embedded in the CA3 network model. Three patterns were chosen at random, and one test pattern was designed to be easily visualized. The stimulus from the cortex, which simulates the auditory click, excited the test pattern. When only one pattern was embedded in the network and there were no other sources of noise, the test pattern was perfectly recalled. However, when all four patterns were embedded in the network, synapses were shared among the patterns. These shared synapses disrupted the recall of any one of the patterns (MacGregor 1991). The signal in this case was the perfect recall of the test pattern. Noise was represented by disruptions in the recall of this pattern (see Modulatory effect of dopamine, Sect. 2.2, below). How these connections came about, or learning, was not addressed with this model.

2.4 Modulatory effect of dopamine

In our model, dopamine was responsible for modulating the response of cells to excitatory input. To be consistent with electrophysiological studies of dopamine, the effect of dopamine in the model modulated the cells' response to incoming signals. In particular, appropriate dopaminergic activation enhanced the recall of information patterns by reducing extraneous noise from cross-talk activations. Our model of dopamine modulated the amplitude of the excitatory postsynaptic potential (EPSP), and the effect was voltage dependent (Fig. 3). The size of the EPSP was increased as the cells' membrane potential, E, approached threshold, Th, and it was reduced as the membrane potential moved away from threshold. The magnitude of this change in EPSP size was defined in Eq. 1 as f_{DA}. If a dopaminergic receptor was activated, the amplitude of subsequent EPSPs was multiplied by f_{DA}.

$$\mathrm{f}_{DA} = \frac{max}{1 + \left[\frac{Th - E}{Th}\right]^{n}} \tag{1}$$

where *Th* represents the cell's threshold to firing, *E* represents the cell's membrane potential, and *max* is the maximum value of the dopamine factor.

The decision as to whether or not a dopamine receptor was activated was determined randomly. For each cell population there was a probability that each cell had an active dopamine receptor. At each time step, for each cell in the population, a random number between zero and one was generated and compared to the probability of there being an active receptor on a cell in that population. If the random number was less than

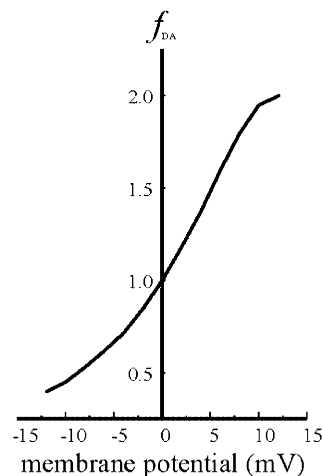

Fig. 3. Dopamine modulated the amplitude of excitatory postsynaptic potentials (EPSPs) by a factor f_{DA}. This modulation was a function of the cells' membrane potential. If a postsynaptic dopamine receptor was activated (see text), the amplitude of the subsequent EPSPs was multiplied by the factor f_{DA}. If the cells' potential was close to threshold, dopamine enhanced the amplitude of the EPSP. If the cells' potential was below the cells' resting membrane potential, dopamine reduced the amplitude of the EPSP. (Resting membrane potential was normalized to 0 mV)

the probability of having a receptor, then the receptor was activated. The conductance change associated with that synapse was multiplied by the dopamine factor, f_{DA}. For these simulations, max was equal to 2.0. Therefore, when the cell was at the resting membrane potential, f_{DA} was equal to 1.0 and dopamine had essentially no effect. This assumption presumed that when a cell was at resting, it was not receiving any information and therefore did not need modulation. The parameter **n** was equal to 2 for all simulations. The effect of dopaminergic modulation was to enhance the cell's response to synchronous input and to decrease its ability to respond to random inputs (Fig. 4).

When only one pattern was embedded in the network (Moxon et al. 2003) and that pattern was stimulated, the pattern was easily recalled (Fig. 4a). However, as more patterns were embedded in the network, it became increasingly difficult to recall the pattern cleanly. Synapses that were shared between the different patterns caused cross-talk disruptions (MacGregor 1991). When four patterns were embedded in the CA3 network (three randomly chosen and one test pattern), the recall was noisy (Fig. 4b). The noise was due to cross-talk activations produced by the other patterns embedded in the network that shared the same synapses. The cells in the network received both excitatory and inhibitory cross-talk activity. This inhibited some cells from firing with the other cells in their link and caused other cells to fire before their time, reducing the synchrony of the response. The modulatory activity of dopamine was chosen to enhance the ability of cells to respond to synchronous input and to discourage them from responding to random input. When 3% of the cells in the network expressed an active dopaminergic receptor at any given time, the poor recall of the pattern was improved (Fig. 4c).

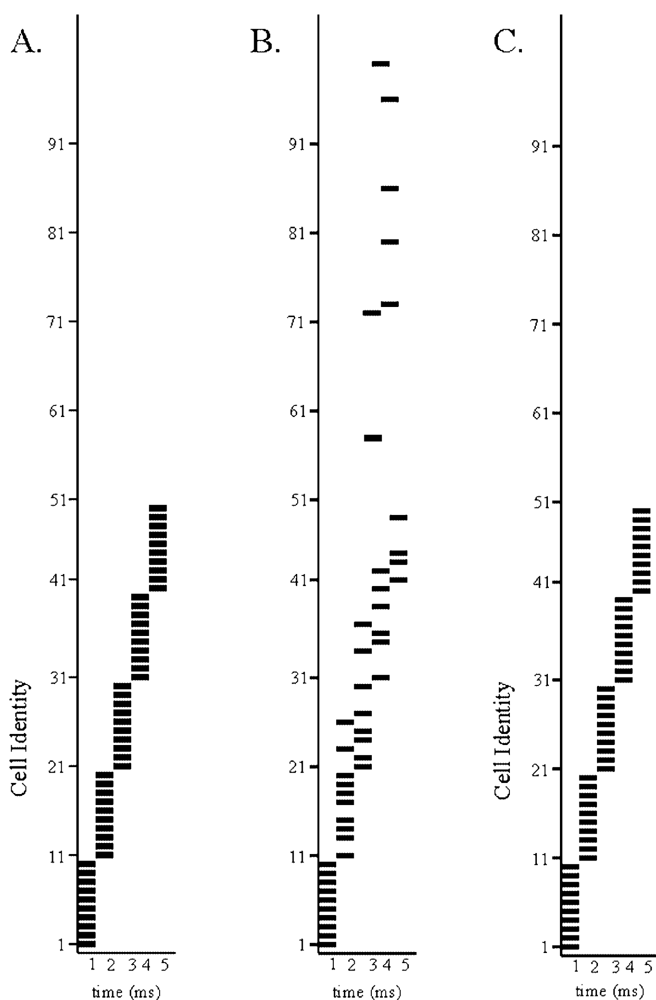

Fig. 4a–c. Recall of information patterns embedded in the local CA3 network. This test pattern was created to be easily visualizable. Cells 1–10 fire at time step 1, cells 11–20 at time step 2, etc. Then the pattern repeated. **a** When only the test pattern was embedded in the network and the network was stimulated, the pattern was easily recalled. **b** When three more patterns were embedded in the network, cross-talk activity caused the recall of the pattern to be noisy. Cells may fire earlier or later than their appointed time, or they may not fire at all. **c** When 3% of the cells in the network expressed an active dopamine receptor, the noise was eliminated and the test pattern cleanly recalled

3 Results

3.1 Effect of dopamine on recall of patterns

When the tone was simulated, both septal and dentate gyrus inputs were added to the entorhinal cortex input that stimulated the test pattern. Under these conditions it was not possible to recall the pattern without some background noise. The signal in this case was defined as specific sets of cells firing in consecutive order (i.e., the test pattern). The noise generated during the recall of a pattern was quantified by summing the number of extraneous cell firings plus the number of missed cell firings (i.e., cells that should have fired at that time but did not due to inhibitory cross-talk interference). When the noise generated during the recall of the pattern was measured as a function of the number of active dopamine receptors, the lowest amount of noise occurred when the number of cells with active dopaminergic sites was between 2% and 4%. Too much or too little dopamine activation increased the noise in the system (Fig. 5).

3.2 Simulation of P50 gating

When the presynaptic effects of $GABA_B$ was incorporated into the model, normal gating was simulated. Connections between cells in the CA3 network were made based on three random patterns and one test pattern, which represented the network's response to the tone. To simulate the conditioning response, nicotinic cholinergic input from the septum excited the cells in the CA3 network. Two milliseconds later, a pattern of information representing the click stimulus entered the hippocampus from the association areas of the cortex through the entorhinal cortex and stimulated the network with the test pattern previously embedded in the network. On average, 3% of the cells in the network

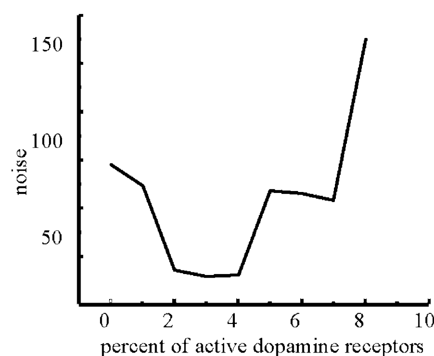

Fig. 5. Effect of increasing postsynaptic dopaminergic activity on S/N. Only small amounts of dopamine were necessary to improve the S/N ratio. When the number of active postsynatpic dopamine receptors was 2%–4% of the population, the noise, defined when the pattern was recalled, was at a minimum. Less or more dopamine increased the noise in the system. The signal was the test pattern displayed in Fig. 4a. The noise was a measure of the number of cells that fired early, late, or not at all. Increased noise implied more cells that did not fire synchronously with the other cells in their link. Decreasing noise implied more cells fired synchronously, as was defined by the embedded pattern

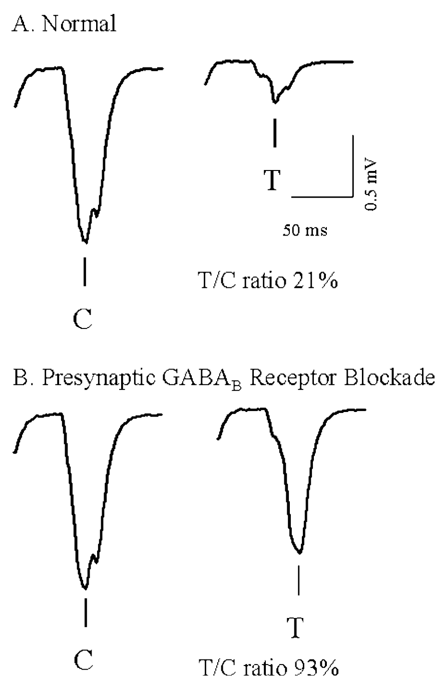

Fig. 6a,b. Computer simulations of the P50 auditory-evoked potential to two paired-click stimuli. Dopaminergic modulation was fixed at 3% (i.e., 3% of the cell had active dopamine synapses at each time step). An active dopamine synapse modulated the amplitude of incoming EPSPs as defined by Eq. 1. **a** Normal gating was simulated by increasing cholinergic activity from the septum and stimulating one of the four patterns embedded in the network via the entorhinal cortex input. The test response was modeled by reducing the cholinergic input to half of the input during the conditioning response and decreasing the excitatory postsynatpic potential by half to simulate presynaptic $GABA_B$ activity. The ratio of the test response to the conditioning response was 21%. **b** When presynaptic $GABA_B$ receptors were blocked, the amplitude of the test response increased, reducing sensory gating to 93%

at any given time expressed the modulatory effects of dopamine defined by Eq. 1. The pattern was recalled and generated a simulated P50 auditory-evoked potential. During the test response, the amount of cortical stimulation and dopaminergic modulation remained the same. The cholinergic input was reduced by 50% and the dentate gyrus input by 75%. In addition, the presynaptic $GABA_B$ mechanism was initiated in response to nicotinic cholinergic input during the conditioning response that reduced the excitatory postsynaptic potentials by 50%. The result was a reduced simulated P50 evoked potential (Fig. 6A). The ratio of the test response to the conditioning response was 21%. To simulate a $GABA_B$ antagonist, the $GABA_B$ mechanism was blocked (Fig. 6b). The amplitude of the test response was greatly increased, and gating was reduced to 93%.

3.3 Effect of blocking nicotine and simulating a nicotinic agonist

When the nicotinic cholinergic input was blocked, there was a smaller simulated response of the network to the conditioning click and a larger simulated response to the test click (Fig. 7b) when compared to the normal case (Fig. 7a). In response to the test stimulus, when nicotinic receptors were blocked, the $GABA_B$ mechanism was not initiated because of a lack of nicotinic input during the conditioning response, and therefore there was a larger simulated test response than in the normal case. The result was a loss of simulated gating due to a decrease in the conditioning amplitude and an increase in the test amplitude. The ratio of the test response to the conditioning response was 64% (Fig. 7b). This result was consistent with both the animal model (Luntz-Leybman et al. 1992; Bickford and Wear 1994, 1996) and with human studies of the effects of nicotine on sensory gating (Adler et al. 1992, 1993).

Next, we simulated a nicotinic agonist by activating the nicotinic cholinergic receptors throughout the simulation (Fig. 7c). The nicotinic cholinergic input was increased at the start of the simulation and remained at the same level throughout. The conditioning amplitude was increased as compared to the conditioning amplitude when nicotinic receptors were blocked. To simulate the test response during a nicotinic activation, the nicotinic cholinergic input was the same level as the conditioning input and lasted throughout the simulation. The $GABA_B$ mechanism was restored due to the restoration of nicotinic input during the conditioning response. The result was a decrease in the test amplitude when compared to the test amplitude when the nicotinic receptors were blocked.

3.4 Blocking nicotinic input and increasing dopaminergic neurotransmission

When the nicotinic input was blocked and the dopaminergic input increased, the amplitudes of both the

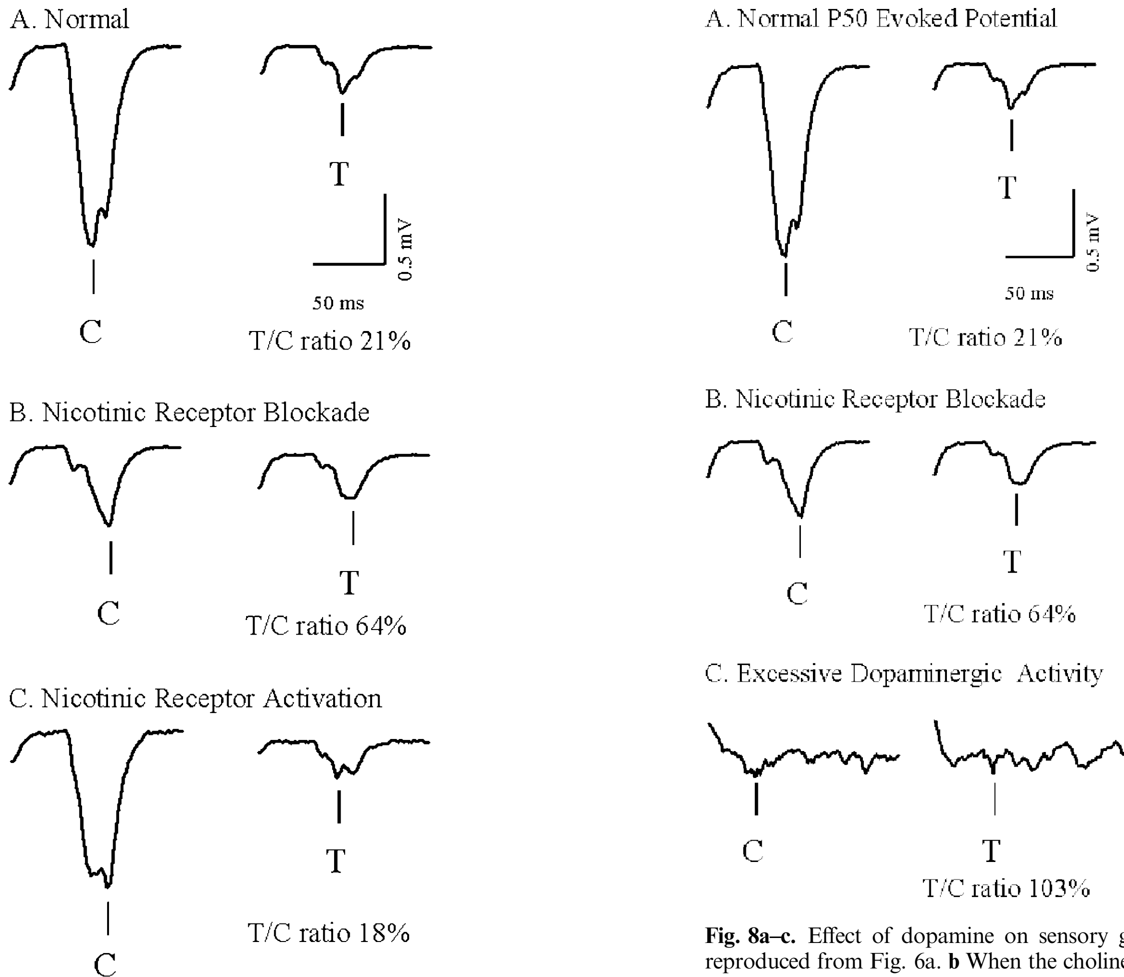

Fig. 7a–c. Effect of modulating nicotinic cholinergic activity in the model. **a** Normal gating reproduced from Fig. 6a. **b** Blocking nicotinic receptors in the model reduced sensory gating by producing a large decrease in the conditioning amplitude as compared to the normal case presented in a. **c** Simulating a nicotinic agonist by activating nicotinic cholinergic synapses throughout the simulation restored gating to 18%

Fig. 8a–c. Effect of dopamine on sensory gating. **a** Normal gating reproduced from Fig. 6a. **b** When the cholinergic input was removed, gating was reduced and the amplitude of the conditioning and test responses were similar. **c** To simulate the response of nonmedicated schizophrenic patients, active dopaminergic synapses in the model were increased from 3% to 8% of the cells in addition to removal of nicotinic input. This resulted in reduced amplitudes of the simulated evoked potentials to both the conditioning and test click stimuli as compared to the loss of nicotine alone shown in **b**

conditioning and test responses were decreased (Fig. 8). The top trace shows normal gating as described above. The second trace shows the effects of blocking nicotinic cholinergic input, also described above. When the number of cells expressing the modulatory effect of dopamine was increased to 8% and nicotinic input was blocked, there were two sources of noise in the system. First, the input from the cortex was noisier because of excessive dopamine in the cortical circuits. Second, the local CA3 network did not respond as well to the input. In this case, the amplitudes of both the conditioning and the test response appeared diminished (bottom trace). This was due to the increased noise before and after the tone in the simulated EEG signal and a noisier signal during the response. This response was similar to the responses of nonmedicated schizophrenic patients who had a deficit in nicotinic cholinergic neuronal transmission and excessive dopaminergic neuronal transmission (Siegel et al. 1984; Waldo et al. 1988; Adler et al. 1982).

4 Discussion

In this paper, we used a computational model of the CA3 region of the hippocampus developed in the companion paper (Moxon et al. 2003) to test the hypothesis that excessive dopaminergic activation can reduce the amplitude of the CR and TR of the P50 auditory-evoked potential to a simulated auditory click stimulus. The model presented tested the hypothesis that dopaminergic activity was a candidate mechanism for reducing the S/N during information recall and ultimately produced smaller amplitudes of the CR and the TR. The model then explored the effects of a combined cholinergic and dopaminergic deficit on sensory gating. While this sensory gating deficit is important because it examines how dysfunction in multiple neurotransmitter systems can affect fundamental sensory processing, it is clear that the dysfunction in dopamine that affects schizophrenic patients also involves many other structures in the brain (Carlsson et al. 2000; Grace 2000; Benes 2000; Lewis 2000) and other neurotransmitters in addition to

dopamine (Aghajanian and Marek 2000; Wassef et al. 1999; Tamminga et al. 1999; Javitt and Zukin 1991).

Data from human studies suggest that schizophrenic patients have at least two abnormalities in sensory processing that can be measured by the P50 auditory-evoked potential, only one of which is reversible by neuroleptics (Adler et al. 1990). The first abnormality is a deficit in sensory gating in the P50 conditioning-testing paradigm. This deficit was insensitive to neuroleptics and was shown to be familial. Schizophrenic patients and about half their first-degree relatives have this same deficit (Siegel et al. 1984; Waldo et al. 1988). The second deficit is the decreased amplitude of the P50 evoked potential and is a state deficit. This deficit was reversed by neuroleptics (Freedman et al. 1983; Adler et al. 1990) and compounds the chronic failure of sensory gating. The combination of these deficits may lead to sensory flooding in acute schizophrenia. Others (Zubin and Spring 1977) have proposed this combination of state and trait abnormalities in acute psychosis. It may not be intuitively obvious why smaller P50 amplitudes represent a second form of hypersensitivity to stimuli in addition to the failure in sensory gating. Dopamine in animals and in humans has been shown to increase neuronal responsivity to excitatory synaptic inputs (Bodis-Wollner et al. 1978; Johnson et al. 1983). If neuronal responsivity is too high, the amplitude of the evoked potential may decrease because the hyperresponsive neurons were more apt to respond to extraneous or random inputs, creating a high level of background noise in the neuronal circuits.

Our model provided an explicit mechanism to account for these neuronal deficits in schizophrenia. Results from the model suggested how the cholinergic input controlled the transfer of sensory information from the cortex into the CA3 hippocampus. The nicotinic cholinergic input to the CA3 network during the conditioning response was necessary in order for the cortical input to excite the network with the pattern. $GABA_B$ activity that suppressed the test response was mediated by nicotinic cholinergic input as well (Moxon et al. 2003). The inclusion of presynaptic $GABA_B$-R to the model enhanced our earlier model of nicotinic cholinergic input alone (Flach et al. 1996). The results presented here suggest that dopamine enhanced the recall of information patterns embedded in the local network by increasing the S/N ratio of the network. It modulated the response of individual cells by enhancing their ability to respond to synchronous input and decreased their ability to respond to random input.

The model suggests that this noise in the hippocampal circuit is of two types. The first is a reduction of the synchronous activation of neurons normally associated with the recall of information patterns. This noise reduced the amplitude of the evoked potential because synchronous activity was required to create the large amplitude response. In the model, the lack of synchronous activity was due to inhibitory cross-talk activation of cells in the pattern so that they were unable to fire with other cells in their link. A second source of noise, which was continually present, was cross-talk activation of cells not in a sensory pattern. This activation occurred when there were too many active dopamine receptors. The result was to raise the background amplitude of the EEG such that even when a signal was produced, as in the responses to the click stimulus, it was not seen above this noise level. The simulation of dopamine blockade as a model for neuroleptics' effects on the system reversed this increased neuronal activity, thereby restoring synchrony and normalizing the amplitudes.

The reduced synchronous activity due to inhibitory cross talk was dominant when dopaminergic activity was very low. As dopamine action increased above an optimal level for maximizing the S/N, activation of cells outside the pattern became dominant. It is intriguing to speculate that the negative symptoms of schizophrenia are a result of this inhibitory cross talk in our model, while the positive symptoms of schizophrenia are in response to excitatory cross-talk activation. The positive symptoms of schizophrenia have been associated with hyperactivity of subcortical dopamine systems (Angrist and Van Kammen 1984; Deutch 1992, 1993; Weinberger 1987; Gray et al. 1991), while the negative symptoms have been associated with hypoactivity of cortical circuits possibly due to desensitization of postsynaptic dopamine receptors (reduction of postsynaptic dopaminergic activity). The negative symptoms of schizophrenia are characterized by avolitioin and flattened affect and have been hypothesized to be the result of an inability to properly form intentions, as a result of which actions are rarely elicited (Frith 1987). Perhaps the inhibitory cross talk seen in our simulations with low levels of dopamine activity is the neural correlate of patients' inability to properly recall stored neural patterns or programs for initiating activity, resulting in these negative symptoms. The postive symptoms of schizophrenia are characterized by increased distractability (Crow 1980) and have been hypothesized to result from an inability to disattend to irrelavent stimuli (Sarter 1994). The activation of large numbers of cells belonging to associated patterns (patterns that share synapses) is then a neural correlate for less discriminative attention.

Other investigators have suggested a role for dopamine in filtering (Joseph et al. 1979) or in maintaining a high S/N ratio in local neural circuits. A connectionist model of dopamine's modulatory effect on behavior was presented by Servan-Schreiber et al. (1990) and shown to be relevant to schizophrenia (Cohen and Servan-Schreiber 1992). Their model examined the effects of dopamine on behavior during cognitive tasks and showed how a decrease in dopamine could be responsible for certain cognitive deficits associated with schizophrenia. Our model was at the cellular level and was used to examine the neuronal circuits that may be involved in a conditioning-testing deficit. The modulatory effect of dopamine was consistent with data on the postsynaptic effects of dopamine, and the model included parameters that are measurable. In particular, this dopaminergic model was based on parameters of the neuron itself. Hence it is the state of the neuron that controlled the effect of the dopaminergic input. In addition, the role

dopamine played in signal transduction was to enhance the ability of the cell to respond to synchronous input and disregard random activation as defined by modified Hebb cell assemblies. These cell assemblies were chosen because they were consistent with data from multiple, single-unit electrophysiological experiments (Nicolelis et al. 1993, 1995; Eggermont 1993, 1994; Gochin et al. 1994). In addition, our model is built at the neuronal, rather than the behavioral, level. Recording the firing patterns of cells simultaneously recorded with chronic-electrophysiological electrodes can test our model. If two or more cells are simultaneously recorded that are part of the same active pattern being recalled in the network, cross-correlation analysis of these cells' activity should show a strong correlation between the two cells. As the noise in the network increases due to increased dopaminergic neuronal transmission, the cross correlation should spread out and become more flat as the synchrony of firing is diminished.

In summary, the results from our model suggest a way in which septal nicotinic cholinergic input to the hippocampus enhances the network's response to the conditioning click stimulus entering from cortical regions. The nicotinic cholinergic input increased activity of local interneurons in the network, which activated presynaptic $GABA_B$ receptors. The increased presynaptic $GABA_B$ activity decreased the network's response to the test tone. Normal amounts of dopaminergic modulation in the cortex and hippocampus increased the synchrony of the response of the network. However, too much or too little dopamine modulation decreased the synchrony of the response, thereby increasing background noise in the circuit. This reduction in the S/N results were consistent with electrophysiological recordings in an animal model (Bickford-Wimer et al. 1990; Luntz-Leybman et al. 1992) and data from human studies (Adler et al. 1990, 1992, 1993; Freedman et al. 1983, 1987) and could help to explain both the positive and negative symptoms of schizophrenia.

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