Modeling the Effects of Nicotine on a Continuous Performance Task

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Abstract. We have developed a neurocomputational model of some attentional effects of nicotine. Our simulations reproduce results showing smoking abstinence to impair performance on a rapid visual information processing task involving detecting sequences of even or odd digits.

Our model treats presence of nicotine as enhancement of modulatory acetylcholine signals, which focus attention on task-relevant stimuli. Our network includes cholinergic signals from nucleus basalis; working memory representations in dorsolateral prefrontal cortex; inputs to nucleus basalis from entorhinal cortex; and recency signals. Digits are represented at entorhinal, nucleus basalis, and dorsolateral levels, along with dorsolateral representations of the concepts "even" and "odd."

Key words: nicotine, acetylcholine, attention, working memory, rapid visual information processing

1. Introduction

Nicotine, like other drugs of abuse such as cocaine and heroin, often leads to short-term increases in positive affect and decreases in negative affect (Gilbert, 1995). However, it is different from these other drugs in its cognitive affects, particularly in its enhancement of attention (most notably, sustained attention) and working memory. The sustained attention task used most often in nicotine-related experiments is the Rapid Visual Information Processing task (RVIP), a type of continuous performance test. In the most common form of the RVIP, visual stimuli (individual digits from 1 to 9) are presented one at a time at a rate of 100 or more per minute at the center of a computer display monitor. Participants press a key whenever three odd or three even digits appear in sequence. Almost all well-designed RVIP studies have found nicotine (delivered by smoking, transdermal patch, or injection) to enhance target detection in habitual smokers (reviewed by Kassel, 1997 and Warburton, 1998).

Nicotine has effects on almost all of the major neurotransmitter systems (see Gilbert, 1995, for review), particularly the cholinergic, dopaminergic, and noradrenergic systems. The close association of this substance with nicotinic cholinergic receptors, and the importance of acetylcholine in selective attention (see, e.g., Kassel, 1997), however, make cholinergic modulation appear to be a particularly important substrate for the attention-enhancing effects of smoking. Hence, in the neural network model we have developed, for parsimony we treat the short-term deficit of recently quitting smokers on attentional tasks requiring continuous performance such as the RVIP as a deficit in cholinergic modulation of systems involved in both attentional and working memory. Dopaminergic and noradrenergic systems will take on more importance when we extend the model to tasks other than the RVIP, and affective states, that are also affected by nicotine.

2. Nicotine and Cholinergic Pathways

There are two major types of acetylcholine receptors: muscarinic (which are more prevalent) and nicotinic. Nicotine is, of course, a nicotinic receptor agonist. Two major sources of cholinergic innervation, involving both types of receptors, are the nucleus basalis of the midbrain, which modulates the neocortex, and the septum, which modulates the hippocampus.

Many investigators have posited that cholinergic modulation has some selective effects on some aspect of working memory. Everitt and Robbins (1997) review evidence indicating that the nucleus basalis cholinergic system contributes to visual attention more than to memory per se. This attentional function seems to span both the nicotinic and muscarinic subsystems, as indicated by data of Muir, Everitt, and Robbins (1995) showing that visual attentional dysfunction from nucleus basalis lesions is reversed both by nicotine and by the muscarinic agonist physostigmine.

There are also behavioral results that partly differentiate functions of the nicotinic versus muscarinic subsystems of the cholinergic system. Granon et al. (1995) injected a nicotinic antagonist (bungarotoxin) or a muscarinic antagonist (scopolamine) into the prefrontal cortex of rats and studied their performance on various maze learning tasks. They found that scopolamine impaired working memory on all tasks but bungarotoxin only on tasks requiring responses different from prevailing ones. Granon and her colleagues concluded that "Nicotinic transmission appears to be important in delayed response tasks requiring effortful processing for response selection, while the muscarinic system is involved in general working memory processes" (p. 139). In humans, Rusted et al.

(1998) found that nicotine enhanced recall of words that were semantically related to a prime but not of words that followed the prime automatically.

Since both prefrontal cortex (especially its dorsolateral part) and hippocampus are important areas in working memory, the effects of nicotine and other cholinergic agonists on working memory could operate through either the nucleus basalis-prefrontal or the septohippocampal cholinergic pathways. Newman and Grace (1999) review evidence that prefrontal cortex is more directly involved with working memories for specific stimuli, rewards, and potential behaviors, whereas hippocampus is involved with memories for contexts. Hironaka et al. (2001) studied acetylcholine efflux from both of those regions in rats. They concluded that prefrontal acetylcholine is related to working memory, which they defined in animals as "trial-unique memory of to-be-remembered items," whereas hippocampal acetylcholine is related to reference memory, defined as memory of consistent response rules. In general, nicotine has been found to have a stronger effect on working memory than on reference memory (Levin, Kaplan, & Boardman, 1997).

This combination of results from both rats and primates suggests to us that in the RVIP task, the hippocampus should store representations of contexts including the context of the experimental task itself. The dorsolateral prefrontal cortex should store representations of the specific stimuli relevant for the current task, in this case, odd and even digits and the previously learned concepts of "odd" and "even" themselves. Such a role for the prefrontal cortex is analogous to roles for the rat cortex reviewed by Sarter, Givens, and Bruno (2001), who found that lesions of cholinergic projections to the cortex lead to profound impairments in sustained attention. On a task such as the RVIP, sustained attention requires a focus on the presence or absence of stimuli relevant to the current task. We propose on the basis on the results we have discussed that this focus is achieved through selective enhancements within the set of dorsolateral prefrontal working memory representations of those loci that represent task-relevant stimuli.

Our model, specific to the RVIP task, includes network analogs of the nucleus basalis, and we posit that cholinergic modulation from that region selectively enhances the task-relevant working memory loci in the dorsolateral prefrontal cortex. How the decision is made, on the basis of the experimenter's instructions, as to which loci are task-relevant (and therefore are enhanced) we leave to future extensions of our model. Based on the role of the hippocampus in setting contexts and episodes, we expect that this type of decision is mediated by the septohippocampal cholinergic pathways, including nicotinic pathways.

3. The Neural Network Model

Figure 1 shows the network we have designed to simulate the effects on RVIP of nicotine. It is assumed that nicotine has an agonist effect on nicotinic cholinergic activity. This is a network which combines some modules representing brain areas and other representing memory activations of particular target patterns (in this case, digits) or categories of these targets.

The digits 1 through 9 (0 is typically not included in the RVIP digit display) have representations in three different areas. The first area is the entorhinal cortex, gateway from the sensory cortices to the hippocampus, where the representations are labeled ei, i = 1 to 9. Entorhinal is also one of the chief areas of afferent input to the cholinergic nucleus basalis (Mesulam & Mufson, 1984). These same digits have representations at nucleus basalis, labeled ni. Finally, these digits have working memory representations in dorsolateral prefrontal cortex, labeled di. These di compete via lateral inhibition with one another and with a generic dorsolateral representation D for random inputs other than the digits. Excitatory signals to di nodes from digit inputs are modulated by corresponding ni, so that the amount of cholinergic activation determines attentional biases toward relevant (digit) inputs. Odd and even digit nodes are also in positive feedback with dorsolateral representations for the concepts of "odd" and "even." The dorsolateral representations for the abstract concepts of "odd" and "even" are each activated by dorsolateral nodes for the corresponding digits. Cholinergic signals modulate the connections from digit nodes to odd and even nodes, mimicking the ability of nicotine to enhance attention to the concepts (in this case, odd and even) relevant to the current task. We assume the hippocampal episode representation encodes the current task or rule which biases cholinergic modulation by determining which inputs are relevant, but do not incorporate this effect explicitly into the network equations.

Connections from odd and even nodes to a response node (perhaps somewhere in premotor cortex), labeled R, constitute a third locus of cholinergic modulation from the nucleus basalis nodes ni, The "three in a row" rule is not explicitly incorporated; rather, a key press is interpreted as occurring when response node activity is above a given threshold. Based on the rule instructions (presumably relayed by the hippocampus), connections from the odd (O) and even (E) representations to the response (R) representation are strengthened by cholinergic modulation. Each input of an even or odd digit increases R activation, and the threshold for an actual response (key press) is the amount of activation obtained by excitation from three digits. But every switch from even to odd or odd to even

activates a "recency" representation r that inhibits the response node, reducing its activation back to a baseline level. The recency node is inspired by work of Brown and his colleagues, which hints that there are cells in the rhinal cortex that discriminate familiarity, recency, and novelty (Bogacz, Brown, & Giraud-Carrier, 2001). These investigators distinguish novelty (having never been seen) from recency (having not been seen immediately before the current stimulus).

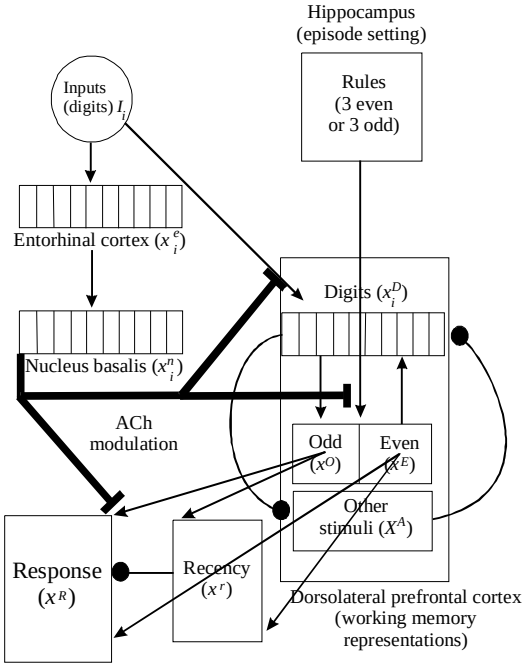

Figure 1. Basic model of brain areas involved in RVIP performance. Arrows denote excitaiton; filled-in circles denote inhibition; bars denote modulation. Cholinergic modulation is assumed to selectively amplify working memory representations of task-relevant inputs (in this case, digits). "Odd" and "even" are abstract representations in positive feedback with nodes for odd and even digits respectively.

The RVIP Data

Our model is based on a study, with female subjects, assessing the effects of quitting smoking on mood, EEG, and attention. All subjects had habitually smoked 7 or more cigarettes per day for the preceding two years, and agreed to receive payment for their participation only if biochemically verified smoking abstinence was achieved across the 31-day abstinence period. Details of the study are provided by Gilbert, McClernon et al. (2002) and RVIP, EEG, mood, and individual difference findings are reported in Gilbert et al. (submitted).

Phase 1 was a 5-week duration baseline during which all participants smoked at their usual rate and attended weekly experimental sessions and biweekly monitoring sessions. After the completion of Phase 1, individuals were randomly assigned to the quit group (70% chance) or the smoke group (30% chance) that continued to smoke during the 31-day required abstinence period of the quit group. Phase 2 differed across the two groups only in terms of whether or not the participant smoked. Experimental sessions were held on days 3, 10, 17, and 31 of abstinence (or corresponding time for the smoke group).

The RVIP Task consists of successive vertical presentation of digits (not including 0) on a computer screen for 15 minutes. Digit presentation rate was 116/minute. These digits included 160 target sequences consisting of three even or three odd digits in a row. The subject was instructed to press a particular key on the computer whenever he or she noticed such a target sequence.

Figure 2 shows the results from Gilbert et al. (submitted) on this task. Note that smokers who continue to smoke detect around 120 of the 160 target sequences, whereas smokers who quit average 100 to 110.

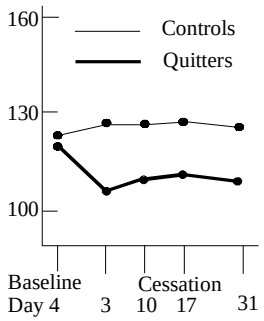

Figure 2. Graph of the comparison between quitters and continuing smokers on the RVIP test.

4. Simulation Results

The simulations are repeated for three different values of theta (5.0, 5.5 and 6.0), corresponding to the different levels of nicotine ingestion. The lower theta values represent lesser nicotine ingestion, that is, the smoker has abstained a greater number of days from smoking. Consistent with the experimental data, as theta values lower, the network performance grows worse at detecting triplets of odds or evens.

For all three simulations, the following sequence of 200 digits is generated using a pseudo random number generator in MATLAB, and input in the network. In all three instances, the random number generator is started with the same seed. The most recent digit is the first in the list. As shown below in underline, there are a total of 21 triplets of odd or even digits.

7 5 6 1 4 6 5 8 9 3 7 4 2 7 5 2 8 1 9 8 4 1 5 7 2 5 8 3 7 1 2 5 3 4 9 5 6 2 3 6 4 2 3 9 4 8 5
2 4 6 1 9 2 6 5 3 1 6 2 8 7 2 6 4 7 8 5 9 7 8 6 9 8 4 7 1 3 4 9 7 6 4 2 9 5 7 8 6 4 5 6 9 7 4
8 1 7 2 5 6 3 9 5 4 2 7 9 2 8 6 3 8 1 6 4 9 2 1 3 9 8 3 7 2 5 7 2 4 1 7 4 2 1 6 4 1 5 6 2 4 7
3 2 4 9 7 8 4 1 6 7 4 6 7 3 4 9 5 6 2 1 7 3 8 9 6 5 7 6 3 5 4 6 5 8 4 5 7 2 4 5 7 8 2 4 5 1 6
2 8 1 9 4 7 8 5 1 7 6 9

The following diagrams illustrate several panels showing activations of network nodes on the Y-axis and time on the X-axis. The 3 columns with 9 panels each show activations in nodes representing digits 1 through 9. Starting from left, the columns represent nodes in entorhinal cortex, nucleus basalis, and dorsolateral prefrontal cortex. The rest of the panels (scanning first horizontally and then vertically) show activations in the odd and even nodes; step response (response above a certain threshold); activations in the recency and response nodes; and a random number generated every time unit (used for simulating distraction due to lack of nicotine ingestion). Each spike in the "step response" graph indicates that the network actually detects an even or odd triplet and responds with a key press.

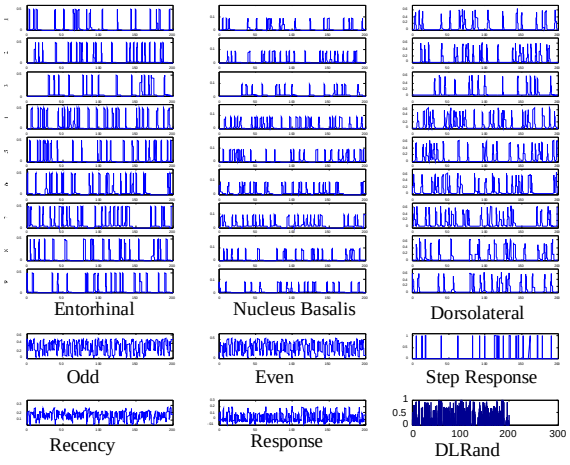

Figure 3. Simulation results for X = 6.0. As the spikes in the graph of "Step Response" indicate, the network detects all 21 triplets of odd and even digits. (But sometimes with higher values of theta it falsely detects a triplet when there are only two odds or evens in a row.)

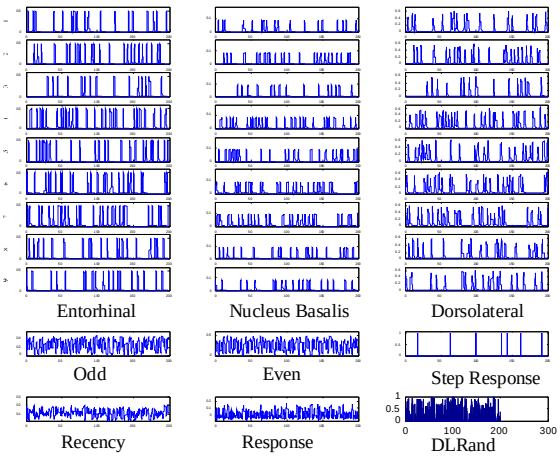

Figure 4. Simulation results for X = 5.0. As the spikes indicate, with low theta values, the network detects a few of the triplets of odd and even digits. Specifically, in this case it detects 7 out of 21.

For the intermediate value X = 5.5, the network detects 14 triplets out of 21(graph not shown here).

5. Future Extensions of the Model

Coull et al. (1996) found in a PET study that this task increased blood flow in a network of sites in both the prefrontal and parietal cortices involved in working memory and sustained attention. Stein (2001) studied this task using fMRI in chronic smokers under both nicotine and a placebo. He found that nicotine increased activation relative to the placebo only in posterior parietal and occipital cortices and not in prefrontal cortex.

Based on Stein's data, we are now expanding our model to include posterior (parietal and occipital) as well as prefrontal representations of the digit stimuli, both influenced by nicotinic cholinergic inputs from nucleus basalis. Prefrontal representations are more subject to executive influences than posterior representations, as in other recent neurocognitive models (e.g., O'Reilly et al., in press). It seems to us a plausible conjecture that posterior cortex is primary engaged in the sustained spatial attention aspect of tasks such as the RVIP, whereas prefrontal (particularly dorsolateral prefrontal) is primarily engaged in the working memory aspects. Based on the observation that nicotine selectively enhances performance of effortful tasks (e.g., Granon et al., 1995; Rusted et al., 1998), Stein's results hint that the sustained attention aspects of the RVIP task are the most effortful, since they involve 15 minutes of concentration on a relatively unchanging visual scene. The working memory aspects of RVIP are less effortful, since most of us have easy access to the stored facts about which digits are even or odd. We predict that fMRI would show greater effect of nicotine on prefrontal activation for different digit-related cognitive tasks that tax working memory more; for example, if the subject is instructed to press a key when the third digit is equal to the sum of the first two.

Our model also needs to add how the brain decides which environmental stimuli are relevant or irrelevant to the current task. Several experimentalists and theorists have recently suggested such a role for parts of the ventral striatum, especially the nucleus accumbens (Frank, Loughry, & O'Reilly, 2001). The basal ganglia gating mechanism is thought to be influenced by inputs from the amygdala in the case of "hot cognition" wherein task relevance is influenced by strong affect. In the case of "cold cognition," such as following an experimenter's instructions in a task such as the RVIP, a more relevant input to the basal ganglia is from the hippocampus. Newman and Grace (1999) been suggested the hippocampus plays such a regulatory rule for working memory "throughput." This could be a mechanism for the operation of the simplified "hippocampal episode setting" shown in our Figure 1.

Finally, since nicotine affects the noradrenergic and dopaminergic systems as well as the cholinergic, future versions of the model should include effects on all three transmitter systems. Our conjecture once again is that while the RVIP task primarily engages nicotine's cholinergic effects, other cognitive tasks are likely to involve nicotine's effects on one of the other transmitter systems. As for norepinephrine, Kassel (1997) reviewed data suggesting that

norepinephrine and acetylcholine might have distinct roles in sustained attention. Specifically, acetylcholine is involved in narrowing the focus of attention, whereas norepinephrine is involved in increasing processing capacity so that a wider range of stimuli can be selected from. Wider range is not likely to be advantageous in the RVIP. We conjecture that the nicotine-norepinephrine connection is more important for other tasks that involve decisions among a wider range of stimuli, such as distractor tasks (e.g., the RVIP with distractors that Gilbert, Hammersley et al., 2002, studied) or divided attention (Coull, 1998). As for dopamine, there is widespread evidence that nicotine enhances dopaminergic neuron activity in the ventral tegmentum and thereby enhances dopamine transmission in both the nucleus accumbens and the orbitofrontal cortex, among other brain regions. Dopamine is likely to mediate nicotine's negative affect reduction and positive affect enhancement (see Gilbert, 1995). Yet again, dopamine does not appear to be a good candidate for mediating nicotine's effects on the RVIP. Dopamine has most effects on tasks requiring cognitive flexibility (for a review see Ashby, Isen, & Turken, 1999) or response to reinforcing or novel stimuli (e.g., Mirenowicz & Schultz, 1994), neither of which are at a premium on the RVIP.

Thus our conjecture is that nicotine ingestion could operate by raising the release or circulating level of any of these three neurotransmitters, and the requirements of different cognitive tasks activate different combinations of transmitter systems. Also, different tasks tend to generate selective increases in blood flow to particular brain regions such as parietal or prefrontal cortex. Such task-triggered selective activations could involve feedback from prefrontal executive regions to other brain areas including midbrain modulatory transmitter nuclei (see, e.g., Sarter et al., 2001).

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