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COGNITIVE NEUROSCIENCE

Cholinergic control of cortical network interactions enables feedback-mediated attentional modulation

Gustavo Deco[1] and Alexander Thiele[2]
[1]Department of Technology, Computational Neuroscience, Institució Catalana de Recerca i Estudis Avançats (ICREA), Universitat Pompeu Fabra, Roc Boronat, 138, 08018 Barcelona, Spain
[2]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

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Abstract

Attention increases our ability to detect behaviorally relevant stimuli. At the neuronal level this is supported by increased firing rates of neurons representing the attended object. In primary visual cortex an attention-mediated activity increase depends on the presence of the neuromodulator acetylcholine. Using a spiking network model of visual cortex we have investigated how acetylcholine interacts with biased feedback to enable attentional processing. Although acetylcholine affects cortical processing in a multitude of manners, we restricted our analysis to four of its main established actions. These were (i) a reduction in firing rate adaptation by reduction in M-currents (muscarinic), (ii) an increase in thalamocortical synaptic efficacy by nicotinic presynaptic receptors, (iii) a reduction in lateral interactions by muscarinic presynaptic receptors, and (iv) an increase in inhibitory drive by muscarinic receptors located on inhibitory interneurons. We found that acetylcholine contributes to feedback-mediated attentional modulation, mostly by reducing intracortical interactions and also to some extent by increasing the inhibitory drive. These findings help explain why acetylcholine is necessary for top–down-driven attentional modulation, and suggest a close interdependence of cholinergic and feedback drive in mediating cognitive function.

Introduction

Attention ensures that behaviourally relevant information is processed at the expense of irrelevant information. Neuronal correlates of attention reveal that this is reflected in an up-modulation of firing rates in cortical neurons representing the attended location or object (Moran & Desimone, 1985; Spitzer *et al.*, 1988; Motter, 1993; Miller *et al.*, 1993; Chelazzi *et al.*, 1993; Reynolds & Desimone, 1999; Luck *et al.*, 1997; Chelazzi, 1998; McAdams & Maunsell, 1999), an up-modulation which is already present in V1 (Haenny & Miller, 1988; Roberts *et al.*, 2007; Roelfsema *et al.*, 1998; Chen *et al.*, 2008). The attentional bias itself is generated in areas outside the visual cortex (Moore & Armstrong, 2003; Gregoriou *et al.*, 2009) but fed back to early visual areas. The feedback ensures that cells representing the attended stimulus 'win' over cells representing nonattended stimuli. While the effects of attention on cellular responses have been studied *in vivo* and *in silico*, little is known about their molecular mechanisms. A variety of different neurotransmitters, neuromodulators and receptor mechanisms have been proposed as playing key roles in these effects (e.g. acetylcholine, noradrenaline and NMDA receptors), but their immediate effects on cellular activity during attention remains poorly understood. A growing body of evidence suggests that acetylcholine is part of the neurochemical machinery which enables attentional modulation of cellular responses (Sarter *et al.*, 2005; Furey *et al.*, 2008; Herrero *et al.*, 2008). In particular, Herrero *et al.* (2008) tested how acetylcholine contributes to attentional modulation in primary visual cortex. They combined iontophoretic pharmacological analysis of cholinergic receptors with single-cell recordings in V1 of rhesus macaque monkeys (*Macaca mulatta*) during performance of a task that demanded top–down spatial attention. Small local application of acetylcholine significantly increased attentional modulation in V1 neurons. Using the selective antagonists scopolamine and mecamylamine, Herrero *et al.* (2008) demonstrated that acetylcholine's actions were mediated by muscarinic but not nicotinic receptors.

While this shows that acetylcholine is important for attentional modulation of sensory cortex responses, it does not easily fit with the proposal that attention is mediated by feedback from higher cortical areas (Roelfsema *et al.*, 1998; Moore & Armstrong, 2003; Gregoriou *et al.*, 2009). Also, it is not easy to interpret the data in terms of possible cellular changes that take place, because cellular effects of acetylcholine are multiple and complex (see Hasselmo & Giocomo, 2006; for a review). Just a few of the main effects are as follows. (i) High ACh levels increase the magnitude of afferent input to the cortex through nicotinic receptors located presynaptically on thalamocortical (feedforward) terminals (Gil *et al.*, 1997; Disney *et al.*, 2007). (ii) High ACh levels reduce the magnitude of corticocortical excitatory

Correspondence: G. Deco, as above.
E-mail: gustavo.deco@upf.edu

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recurrent interactions through presynaptic inhibition of glutamate release via muscarinic receptors (Hasselmo & Bower, 1992). (iii) Furthermore, ACh reduces spike frequency adaptation due to its effect on muscarinic (M)-currents (Hasselmo & Giocomo, 2006). Reduced spike frequency adaptation might result in increased stability of stimulus or abstract representations at the single neuron level, which would benefit attentional processing. (iv) Finally, activation of muscarinic receptors results in increased neuronal excitability (McCormick & Prince, 1986), and in V1 these are predominantly expressed on inhibitory interneurons (Disney *et al.*, 2006). This asymmetric receptor distribution would cause a net increase in inhibitory drive when ACh is high, a prediction that at first seems counterintuitive to the notion of the involvement of ACh in attentional modulation.

The multitude of effects of ACh on cortical networks presents a challenge, as complex interactions are likely to occur which together promote attentional modulation. Here, we analyse parametrically how the different ACh components affect attention in a network model of V1, where feedback from other cortical areas provides the attentional signal. We find that, in the presence of feedback from 'higher' areas, the main effect of cholinergic manipulations on attentional modulation is through reduced intracortical interactions in conjunction with an increase in the inhibitory drive within the network.

Materials and methods

The analysis of the attentional modulation of the firing rate of V1 neurons was performed by explicit simulations of a detailed spiking and synaptic model for describing the dynamic transients. Importantly, these simulations enable a direct comparison between the model and neurophysiological data. The simulations of the spiking dynamics of the network were integrated numerically (1000 integrate-and-fire equations, one for each neuron in the network, and simultaneously 2 600 000 AMPA-, NMDA- and GABA-synaptic equations) using the second-order Runge–Kutta method with step size 0.05 ms.

We used leaky integrate-and-fire neurons for modelling the excitatory pyramidal cells and the inhibitory interneurons. The synaptic inputs to an integrate-and-fire neuron are basically described by a capacitor C_m connected in parallel with a resistor R_m through which currents are injected into the neuron. These current injections produce excitatory or inhibitory postsynaptic potentials, EPSPs or IPSPs, respectively.

These potentials are integrated by the cell and, if a threshold θ is reached, a δ-pulse (spike) is fired and transmitted to other neurons, and the potential of the neuron is reset. The incoming presynaptic δ-pulse current from another neuron is low-pass-filtered by the synaptic time constants, and results in an EPSP or an IPSP in the one-compartment neuronal model. We use biologically realistic parameters (McCormick & Prince, 1986). We took for both excitatory and inhibitory neurons a resting potential $V_L = -70$ mV, a firing threshold $\theta = -50$ mV, and a reset potential $V_{reset} = -55$ mV. The membrane capacitance C_m was 0.5 nF for the pyramidal neurons and 0.2 nF for the inhibitory interneurons. The membrane leak conductance g_m was 25 nS for pyramidal cells and 20 nS for interneurons. The refractory period τ_{ref} was 2 ms for pyramidal cells and 1 ms for interneurons. Hence, the membrane time constant $\tau_m = C_m/g_m$ was 20 ms for pyramidal cells and 10 ms for interneurons. In mathematical terms, the dynamics of the sub-threshold membrane potential V of a neuron is given by the equation:

$$C_m \frac{dV(t)}{dt} = -g_m(V(t) - V_L) - I_{syn}(t) - I_M \quad (1)$$

The synaptic currents $I_{syn}(t)$ that flow into the cells are mediated by three different families of receptors. The recurrent excitatory postsynaptic EPSPs are mediated by AMPA and NMDA receptors. These two glutamatergic excitatory receptors are on the pyramidal cells and on the interneurons. The external inputs (background, sensory input, and external top–down interaction from other areas) are mediated by AMPA synapses on pyramidal cells and interneurons. Inhibitory GABAergic synapses on pyramidal cells and interneurons yield the corresponding IPSPs. We considered that the NMDA currents have a voltage dependence that is controlled by the extracellular magnesium concentration (Jahr & Stevens, 1990), $C_{Mg^{++}} = 1$ mM.We neglected the rise time of both AMPA and GABA synaptic currents because they are typically very short (<1 ms). The rise time for NMDA synapses is $\tau_{NMDA,rise} = 2$ ms (Spruston *et al.*, 1995; Hestrin *et al.*, 1990). All synapses had a latency (time delay) of 0.5 ms. The time constant for AMPA synapses was $\tau_{AMPA} = 2$ ms (Spruston *et al.*, 1995; Hestrin *et al.*, 1990), for NMDA synapses $\tau_{NMDA,decay} = 100$ ms (Spruston *et al.*, 1995; Hestrin *et al.*, 1990), and for GABA synapses $\tau_{GABA} = 10$ ms (Salin & Prince, 1996; Xiang *et al.*, 1998). The synaptic conductivities for each receptor type were taken from Brunel & Wang (2001), were adjusted using a mean field analysis to be ~1 nS in magnitude, and were consistent with experimentally observed values (Destexhe *et al.*, 1998). As was noted by Brunel & Wang (2001), Wang (1999) and Lisman *et al.* (1998), the recurrent excitation was assumed to be largely mediated by the NMDA receptors, in order to provide more robust persistent activity during the short-term memory-related delay period; and the amplitude of recurrent excitation was smaller than that of local inhibition, and therefore the net recurrent input (i.e. the sum of these two terms) to a neuron was hyperpolarizing during spontaneous activity (i.e. without external inputs; Brunel & Wang, 2001; Amit & Brunel, 1997). In summary, the synaptic current is given by the sum of glutamatergic-, AMPA ($I_{AMPA,rec}$)- and NMDA ($I_{NMDA,rec}$)-mediated recurrent excitatory currents, one AMPA ($I_{AMPA,ext}$)-mediated external excitatory current and one inhibitory GABAergic current (I_{GABA}):

$$I_{syn}(t) = I_{AMPA,ext}(t) + I_{AMPA,rec}(t) + I_{NMDA,rec}(t) + I_{GABA}(t) \quad (2)$$

The currents are defined by:

$$I_{AMPA,ext}(t) = g_{AMPA,ext}(V(t) - V_E)\sum_{j=1}^{N_{ext}} s_j^{AMPA,ext}(t) \quad (3)$$

$$I_{AMPA,rec}(t) = g_{AMPA,rec}(V(t) - V_E)\sum_{j=1}^{N_E} w_j s_j^{AMPA,rec}(t) \quad (4)$$

$$I_{NMDA,rec}(t) = \frac{g_{NMDA,rec}(V(t) - V_E)}{1 + \frac{[Mg^{++}]\exp(-0.062\,V(t))}{3.57}} \times \sum_{j=1}^{N_E} w_j s_j^{NMDA}(t) \quad (5)$$

$$I_{GABA}(t) = g_{GABA}(V(t) - V_I)\sum_{j=1}^{N_I} s_j^{GABA}(t) \quad (6)$$

where $V_E = 0$ mV, $V_I = -70$ mV, w_j are the synaptic weights, and each receptor has its own fraction s_j of open channels and its own

synaptic conductance g. The values for the synaptic conductances for excitatory neurons are $g_{\mathrm{AMPA,ext}} = 2.08$ nS, $g_{\mathrm{AMPA,rec}} = 0.104$ nS, $g_{\mathrm{NMDA}} = 0.327$ nS and $g_{\mathrm{GABA}} = 1.25$ nS; and for inhibitory neurons $g_{\mathrm{AMPA,ext}} = 1.62$ nS, $g_{\mathrm{AMPA,rec}} = 0.081$ nS, $g_{\mathrm{NMDA}} = 0.258$ nS and $g_{\mathrm{GABA}} = 0.973$ nS. These conductances were calculated so that the excitatory neurons have in the absence of sensory stimulation a spontaneous spiking rate of 3 Hz and the inhibitory neurons a spontaneous rate of 9 Hz (Brunel & Wang, 2001). The fractions of open channels are described by:

$$\frac{\mathrm{d}s_j^{\mathrm{AMPA,ext}}(t)}{\mathrm{d}t} = -\frac{s_j^{\mathrm{AMPA,ext}}(t)}{\tau_{\mathrm{AMPA}}} + \sum_k \delta(t - t_j^k) \tag{7}$$

$$\frac{\mathrm{d}s_j^{\mathrm{AMPA,rec}}(t)}{\mathrm{d}t} = -\frac{s_j^{\mathrm{AMPA,rec}}(t)}{\tau_{\mathrm{AMPA}}} + \sum_k \delta(t - t_j^k) \tag{8}$$

$$\frac{\mathrm{d}s_j^{\mathrm{NMDA}}(t)}{\mathrm{d}t} = -\frac{s_j^{\mathrm{NMDA}}(t)}{\tau_{\mathrm{NMDA,decay}}} + \gamma x_j(t)\left(1 - s_j^{\mathrm{NMDA}}(t)\right) \tag{9}$$

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = -\frac{x_j(t)}{\tau_{\mathrm{NMDA,rise}}} + \sum_k \delta(t - t_j^k) \tag{10}$$

$$\frac{\mathrm{d}s_j^{\mathrm{GABA}}(t)}{\mathrm{d}t} = -\frac{s_j^{\mathrm{GABA}}(t)}{\tau_{\mathrm{GABA}}} + \sum_k \delta(t - t_j^k) \tag{11}$$

where $\gamma = 0.5/\mathrm{ms}$. The sums over k represent a sum over spikes formulated as δ-peaks ($\delta(t)$) emitted by presynaptic neuron j at time t_j^k.

We also implemented spike-frequency adapting mechanisms, including M-currents (Benda & Herz, 2003; Ermentrout, 1998). M-type currents are slow voltage-dependent potassium currents (Brown & Adams, 1980). This current I_{M} in the integrate-and-fire equation is given by:

$$I_{\mathrm{M}} = g_{\mathrm{M}}\, a(t)\,(V(t) - V_{\mathrm{M}}) \tag{12}$$

where V_{M} is the reversal potential of the potassium channel. Because this current is mainly activated by suprathreshold membrane potential, Benda & Herz (2003) proposed implementing M-currents by incrementing the adaptation variable $a(t)$ after each action potential by a small amount (α), so that I_{M} is incremented accordingly. Between spikes the $a(t)$ dynamics are modelled as a leaky integrator with a decay constant τ_{M}. Hence, the dynamics of the M-current can be described by the following system of equations:

$$\frac{\mathrm{d}a(t)}{\mathrm{d}t} = -\frac{a(t)}{\tau_{\mathrm{M}}} \tag{13}$$

$$\text{If } V(t) = V_{\mathrm{thr}}, \text{ then } a(t) = a(t) + \alpha, \text{ and } V = V_{\mathrm{reset}} \tag{14}$$

The $a(t)$ was initially set to be 0, $\tau_{\mathrm{M}} = 100$ ms, $\alpha = 0.05$ and $V_{\mathrm{K}} = -80$ mV. The I_{M} current was present in all excitatory cells but only in 10% of the inhibitory cells, as many inhibitory neurons show limited spike frequency adaptation (McCormick *et al.*, 1985).

In order to adjust the parameters defining the reference working point, we used the mean field approach defined in the appendix of Deco & Rolls (2005).

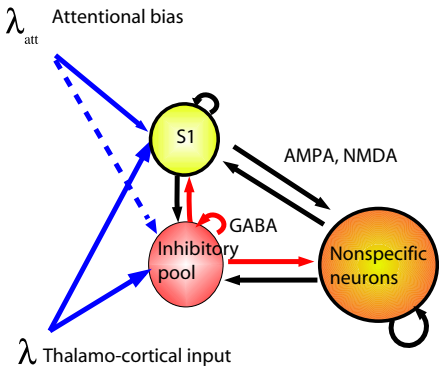

FIG. 1. Spiking network model of feedback attention in V1. The model implements a dynamic interaction between different neurons. The specific types of interaction affect how much the bias introduced by spatially selective attentional input can affect overall firing rates. In our model the bias is assumed to be an attentional feedback signal from higher cortical areas. The neurons are fully connected (with synaptic strengths as specified in the text). Neurons are clustered into two different types of pools: excitatory and inhibitory. There are two subtypes of excitatory pools, selective and nonselective; selective pools encode the visual stimulus. The recurrent arrows indicate recurrent connections between the different neurons in a pool. Thalamocortical inputs targeted the *S1* and the inhibitory pool. Feedback either exclusively targeted the *S1* pool (imagine the dashed blue line in the figure to be absent), or it targeted the *S1* and the inhibitory pool (indicated by the solid and dashed blue line). AMPA connections are plotted in blue, while AMPA + NMDA connections are plotted in black, and GABA connections are plotted in red. For interpretation of color references in figure legend, please refer to the Web version of this article.

Cortical network model

To analyse the evolution of the firing rate of neurons in V1 under attentional modulation, we employed a basic V1 network model. In this model of V1, interacting neurons are organized into discrete populations as depicted in Fig. 1. The model contains two sets of excitatory neuron pools and one set of inhibitory neurons The network contains N_{E} (excitatory) pyramidal cells and N_{I} inhibitory interneurons. In our simulations, we use $N_{\mathrm{E}} = 800$ and $N_{\mathrm{I}} = 200$, consistent with the neurophysiologically observed proportion of 80% pyramidal cells versus 20% interneurons (Abeles, 1991). We assumed that there is a selective population encoding a specific visual stimulus at specific retinal locations (e.g. encoding bar orientation, spatial frequency, and location). In our case, we considered just one selective population, which we denoted *S1*, which was sensitive to the specific visual stimuli used in the experiments. The specific population of excitatory cells contained rN_{E} neurons (in our simulations $r = 0.1$). In addition there was one nonselective population *S2*, which grouped all the remaining excitatory neurons not involved in the present tasks, and one inhibitory population, grouping the local inhibitory neurons and regulating the overall activity by introducing competition into the network. In the experiment considered here, two stimuli would always be presented simultaneously, one stimulus in the receptive field of the neurons that are part of the network model (which reside in one cerebral hemisphere), the other stimulus in the hemifield that is represented not by neurons in our network model but by neurons in the opposite hemisphere. They were ignored in this network model, as the neurons in different hemispheres are not strongly interlinked. This also means that *S2* neurons in our model were not the neurons that represent the stimulus presented in the opposite visual hemifield, but were simply neurons which represent the stimulus location but have little or no feature selectivity for the stimulus presented.

The evolution of the firing rates in the network was properly captured by the spiking and synaptic dynamics of one-compartment integrate-and-fire (IF) neuron models. An IF neuron integrates the

afferent current generated by the incoming spikes, and fires when the depolarization of the cell membrane crosses a threshold. Furthermore, the IF neuronal cells were modelled as having the three types of receptors mediating the synaptic currents flowing into them as described above, namely glutamatergic AMPA receptors, NMDA receptors and gabaergic GABAa receptors. This simulation allowed a thorough study of realistic timescales and firing rates involved in the evolution of the neural activity, which can be quantitatively contrasted with experimental data. Because at this level of detail the model allows the use of realistic biophysical time constants and conductances, it is also possible to investigate which parameters need to change to match the attentional effects that were seen when specific cholinergic receptors were inactivated experimentally (Herrero *et al.*, 2008).

The neurons were fully connected. Full connection was adopted here for simplicity in the implementation but it may not be too unrealistic as the neurons considered would possibly be located within a single V1 column, or in columns that are close together. At the same time it has been shown that a network with more realistic sparse connectivity would yield the same results, because sparsity does not change the dynamic behaviour of the network but just increases the level of the finite-size effect, i.e. it increases the noise. In fact, from a mean-field point of view the fully and sparsely connected networks are equivalent (see Brunel & Wang, 2001 and Mattia & Del Giudice, 2004; for more details). The conductance values for the synapses between pairs of neurons were modulated by connection weights, which could deviate from their default value of 1. The structure and function of the network was achieved by differentially modulating these weights within and between populations of neurons. We assumed that the connections were already formed, e.g. by earlier self-organization mechanisms, as if they were established by Hebbian learning, i.e. the coupling was strong if the pair of neurons had correlated activity and weak if they were activated in an uncorrelated way. As a consequence of this, neurons within a selective excitatory population were mutually coupled with a strong weight w_+. Neurons in a selective excitatory population were connected to neurons in the nonselective population with a synaptic weight $w = 1$ and neurons in the nonselective population were connected to neurons in a selective excitatory population with a synaptic connection of weight $w_- = 1 - \frac{r(w_+ - 1)}{1 - r}$,so that the overall recurrent excitatory synaptic drive in the spontaneous state remained constant as w_+ was varied (Brunel & Wang, 2001). Neurons in the inhibitory population were mutually connected with an intermediate weight $w = 1$. They were also connected with all excitatory neurons with the same intermediate weight which for excitatory-to-inhibitory was $w = 1$ and for inhibitory-to-excitatory connections was w_{inh}. Each individual population was driven by two different kinds of input. First, all neurons in the model network received spontaneous background activity from outside the module through $N_{\text{ext}} = 800$ external excitatory connections. Each connection carried a Poisson spike train at a spontaneous rate of 3 Hz, which is a typical value observed in the cerebral cortex. This resulted in a background external input with a rate of 2.4 kHz for each neuron. Second, the neurons in the specific population additionally received external inputs encoding stimulus-specific information (labelled as thalamocortical input). When stimulating the selective population *S1*, an extra Poisson train to the neurons was applied with rate λ encoding the presence of an effective stimulus for that population. We assumed that this stimulus drive was weighted by a synaptic weight w_{thal} corresponding to thalamocortical connections. Thalamocortical connections also target inhibitory interneurons in layer 4 (Freund *et al.*, 1985, 1989), which was implemented in our model by the fact that the extra Poisson train to the neurons with rate λ encoding the presence of an effective stimulus also drove 10% of the inhibitory neurons. Restricting thalamocortical input to 10% of the interneurons ensured that the proportion of excitatory and inhibitory cells receiving thalamocortical input was also 4:1, thereby reflecting the overall proportion of excitatory and inhibitory cells in the network. Attentional biasing was simulated by selectively boosting the external stimulus drive to the selective excitatory population by an extra value of λ_{att}. This attentional biasing was assumed to be due to feedback from higher cortical areas. Feedback to rodent V1 mostly targets excitatory circuits (Johnson & Burkhalter, 1997). However, it has been shown that feedback can also target inhibitory interneurons (Medalla *et al.*, 2007). To account for this possibility we additionally ran a simulation in which the bias affected not only the specific excitatory pool but also the inhibitory neuronal pool (indicated by the dashed blue line in Figs 1 and 3).

The main purpose of the paper was to explore, within the network model, how the efficacy of this specific feedback (our attentional signal) is affected by alteration of specific cholinergic effects on the excitability of the network. In particular, we were interested in determining which parts of the network are most susceptible to such manipulation, as this analysis will yield insights into the mechanisms by which acetylcholine aids feedback-mediated attentional modulation. The strength of attentional modulation was quantified by calculating the modulation index (MI)

$$\text{MI} = \frac{\text{activity}_{\text{attend RF}} - \text{activity}_{\text{attend away}}}{\text{activity}_{\text{attend RF}} + \text{activity}_{\text{attend away}}} \quad (15)$$

Results

Herrero *et al.* (2008) have recently shown that acetylcholine is part of the machinery of attentional modulation in primary visual cortex (see also Deco & Thiele, 2009). They combined iontophoretic pharmacological analysis of cholinergic receptors with single-cell recordings in V1 while rhesus macaque monkeys performed a task that demanded top–down spatial attention. On a trial-by-trial basis animals were cued whether to attend to the receptive field of the recorded neurons or to the opposite hemifield. Shortly after the cueing, stimuli were presented at the receptive field location and in the opposite hemifield. The animal's task was to detect a subtle change in the stimulus at the cued location and ignore changes in the stimulus at the uncued location. Details of the task and procedures involved have been published previously (Roberts *et al.*, 2007; Thiele *et al.*, 2006). Herrero *et al.* (2008) demonstrated that local acetylcholine application significantly increased attentional modulation in V1 neurons [see Fig. 2A (left histograms) and B], and affected the animal's behavior. Application of scopolamine reduced the attentional modulation, demonstrating that muscarinic receptors were involved (Fig. 2A, right histograms). Mecamylamine application resulted in reduced neuronal gain but did not affect attentional modulation, suggesting that nicotinic receptors in V1 play at most a limited role in attentional modulation (data not shown).

Activation of cholinergic receptors can have multiple, often seemingly contradictory, effects on cortical dynamics (Hasselmo & Giocomo, 2006). Figure 3 graphically summarizes the effect of cholinergic manipulations explored in our network. Figure 3A (right) depicts that high levels of ACh increased the efficacy of afferent thalamocortical input w_{thal} through nicotinic receptors and increased the recurrent inhibitory (w_{inh}) drive, whereas the excitatory (w_+) recurrent interactions and the conductivity of the M-currents g_{M} were

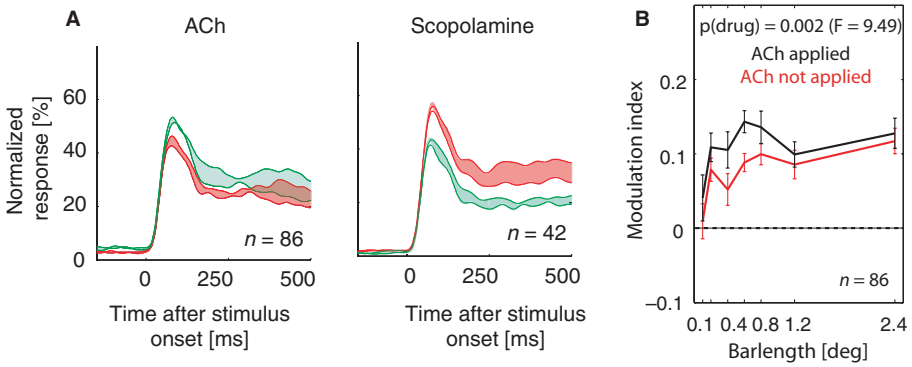

FIG. 2. Drug effects on attentional modulation. (A) Attentional enhancement by application of ACh (left histograms) and attentional decrement by scopolamine (right histograms) for the population of cells. Red curves show the condition when no drug was applied, green curves the condition when the respective drug was applied. The upper curve in each coloured graph shows the 'attend receptive field' condition, the lower curve the 'attend away' condition, i.e. the shaded area between curves shows the strengths of attentional modulation. ACh increased and scopolamine decreased attentional modulation. (B) Quantification of attentional modulation by mean population modulation index (MI) for different bar length with (black line) or without (red line) ACh application (86 cells; error bars denote SEM). Adapted from Herrero *et al.* (2008).

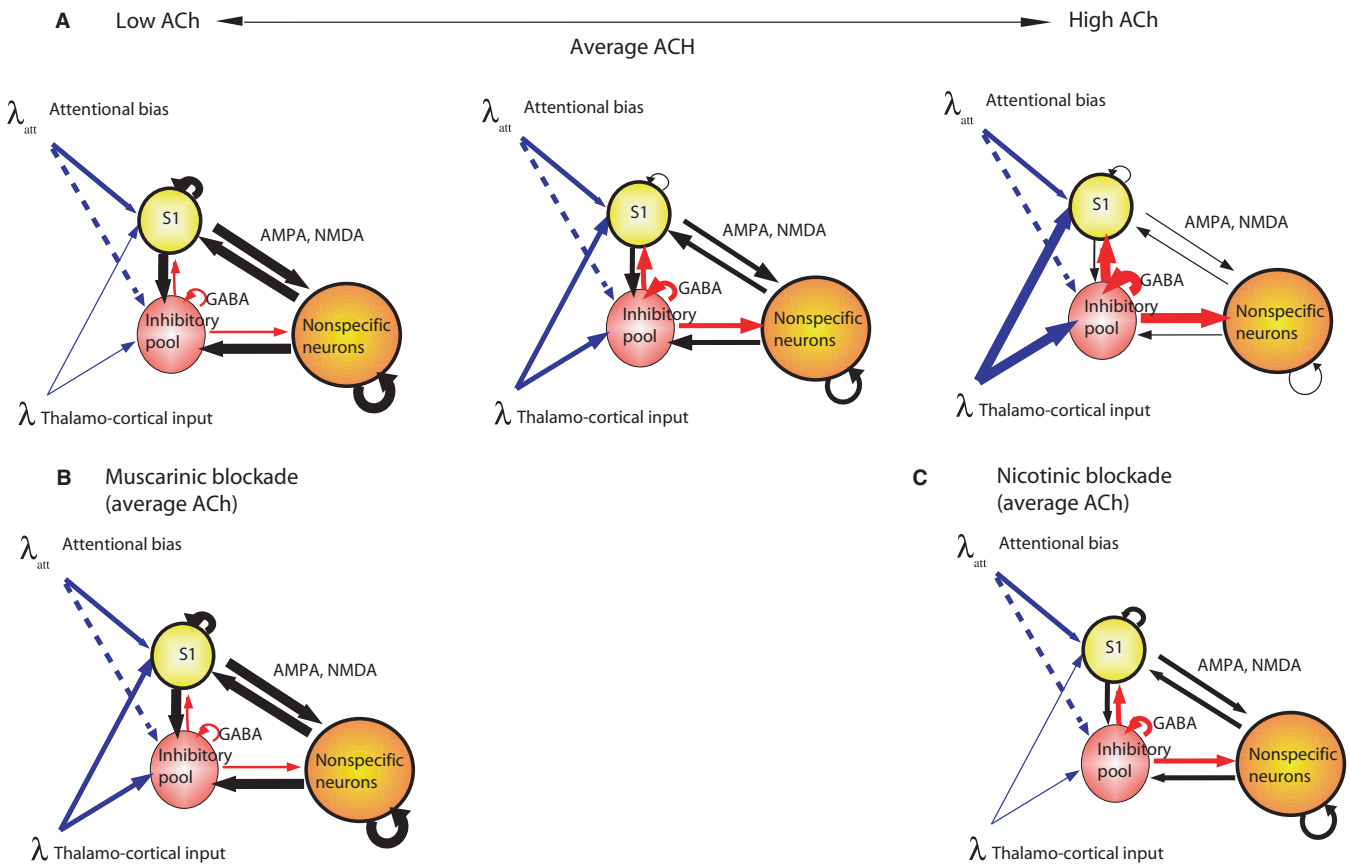

FIG. 3. Cholinergic effect on the cortical dynamics. (A) High ACh levels increased the efficacy of afferent input to the cortex and increase the activity in inhibitory interneurons, thus increasing intracortical inhibition. Moreover, they reduced the efficacy of corticocortical excitatory recurrent interactions and reduced spike frequency adaptation due to reductions in M-currents. For the purpose of comparison, the average ACh level has been replotted to be identical to the one shown in figure 1. (B) The muscarinic antagonist scopolamine resulted in an increase in the excitatory recurrent interactions, an increased spike frequency adaptation and a reduced inhibitory drive. (C) The nicotinic antagonist mecamylamine caused a reduction in the afferent thalamocortical input but left all other parameters unaffected.

reduced. Conversely, for low levels of ACh the efficacy of afferent thalamocortical input w_{thal} and the inhibitory drive w_{inh} was reduced whereas the excitatory (w_+) recurrent interactions and the conductivity of the M-currents g_M were increased (Fig. 3A, left). Application of the muscarinic antagonist scopolamine caused an increase in the excitatory (w_+) recurrent interactions and an increase in the conductivity of the M-currents g_M, whereas the intracortical inhibition (w_{inh}) was reduced (Fig. 3B). Application of the nicotinic antagonist mecamyl-

amine caused a reduction in the afferent thalamocortical input w_{thal} (Fig. 3C). There will be a multitude of additional effects of ACh on cortical networks, but we have intentionally restricted our analysis to a parameter space that can realistically be explored within the framework of this paper.

Our main interest here was to determine how these cholinergic-based changes affect feedback-mediated attentional modulation. In our model we thus parametrically manipulated: (i) the afferent thalamocortical input w_{thal}; (ii) the excitatory (w_+) and inhibitory (w_{inh}) recurrent neuronal interactions; and (iii) the conductivity of the M-currents g_M. For the ACh-based changes in spike-frequency adaptation we considered that all excitatory neurons show M-current-based spike-frequency adaptation, while we assumed that only 10% of the inhibitory neurons have spike-frequency adaptation, because many inhibitory neurons show limited spike-frequency adaptation (McCormick *et al.*, 1985). All these changes were applied locally to the populations manipulated pharmacologically, which correspond to the specific excitatory and inhibitory population associated with the attended location. We performed simulations of the experimental paradigm of Herrero *et al.* (2008) described above. Each simulation began with a period of 500 ms during which no stimulus was presented, to allow the network to stabilize. Then, during a period of 700 ms, a stimulus to the selective population (λ = 8000 Hz = 80 Hz × 100 synapses) was added. Two cases were compared: with and without attention. In the case with attention, an extra attentional bias (λ_{att} = 100 Hz = 1 Hz × 100 synapses when feedback was restricted to excitatory neurons, and λ_{att} = 800 Hz = 8 Hz × 100 synapses when feedback was applied to both excitatory and inhibitory neurons) was added to the selective population, corresponding to the fact that its spatial location was attended. In the case without attention, no bias was applied. The evolution of the spiking activity was averaged over 1000 trials initialized with different random seeds. To evaluate the attentional effect of these manipulations, we calculated the attentional modulation index $= \frac{rate_{att}-rate_{noatt}}{rate_{att}+rate_{noatt}}$, which normalizes explicitly for firing rate. The values of $rate_{att}$ and $rate_{noatt}$ corresponds to the integral of the firing rate curve between 700 and 1000 ms (i.e. 200–500 ms after stimulus onset) for the cases with and without attention, respectively. The results of these simulations for two different network configurations as a function of different parameter settings (strengths of thalamocortical input w_{thal}, excitatory recurrent interactions w_+, inhibitory recurrent interactions w_{inh} and M-currents g_M) are shown in Fig. 4. The left column shows the scenario where feedback only targets the *S1* pool (i.e. feedback is restricted to excitatory neurons). An increase in the afferent thalamocortical input w_{thal} reduced the attentional modulation (Fig. 4A). An increase in the excitatory recurrent interactions w_+ also reduced the attentional effect (Fig. 4B). An increase in the inhibitory weights increased attentional modulation (Fig. 4C). Finally, a reduction in the conductivity of the M-currents g_M, thereby reducing spike frequency adaptation, had little effect on attentional modulation (Fig. 4D).

The right column of Fig. 4 shows the scenario where feedback targets the *S1* (excitatory) and 10% of the inhibitory neuronal pool. Some of the effects for this network configuration are qualitatively similar to the ones described above (although quantitative differences are apparent; Fig. 4E–H). Differences are seen between the two network configurations when effects of inhibitory drive and to some extent spike frequency adaptation are analysed. Altering inhibitory drive had less of an effect on attentional modulation, when feedback terminated on inhibitory and excitatory neurons, compared to when it exclusively terminated on excitatory neurons. Reduction in spike frequency adaptation slightly increased attentional modulation in a network where feedback terminates on *S1* excitatory and on inhibitory neurons (Fig. 4H), but overall the effects of spike frequency adaptation were very small.

From the last analysis it is clear that increasing the level of ACh, or decreasing its effect on muscarinic or nicotinic receptors (by means of scopolamine or mecamylamine application), caused differential effects on feedback-mediated attentional modulation. The differences arose as each pharmacological manipulation specifically affected at least one of the modelled parameters. However, from the analysis it is also apparent that all parameter manipulations have well defined effects on feedback-mediated attentional modulations, i.e. monotonic functions are adequate to describe these effects. In order to be consistent with the experimental results published by Herrero *et al.* (2008), we had to assume that the neuropharmacological manipulations were affecting the w_{thal}, w_+, w_{inh} and g_M parameters within a very specific range. In particular, increasing the ACh level modestly, which resulted in an increase in attentional modulation experimentally, would have to reduce the excitatory recurrences w_+ such that the model output yielded an attentional modulation that matched experimental results. ACh increases would also affect the other parameters w_{thal}, g_M, and w_{inh}, which each would have an effect on attentional modulation on their own. Specifically, raising nicotinic receptor activation (altering w_{thal}) would counteract any attentional increases caused by alterations in w_+, w_{inh} and g_M. It was thus necessary to find a parameter space within which the combined effects were in line with the V1 results (Herrero *et al.*, 2008). It was equally important to determine that a parameter configuration mimicking the experimental results was not a rare local maximum (or minimum) which was flanked by parameter configurations that yielded the opposite result. Although the latter is unlikely given the monotonic functions shown in Fig. 4, we nevertheless explored a variety of parameter configurations and their influence on feedback-mediated attentional modulation. We found that a fairly large sample of parameters yielded feedback-mediated attentional modulation that was within the range of what was found experimentally. The results are shown in Fig. 5. Here we increased w_{thal} in steps of 5% from its basic position (the basic position was supposed to mimic normal cholinergic drive in a task-performing animal), and also altered w_+, w_{inh} and g_M in steps of 5% from their starting position. Note, however, that w_+ and g_M would decrease in 5% decrements while w_{inh} would increase in 5% increments as cholinergic drive increases the latter. For each of these settings we calculated the feedback-mediated attentional modulation over 500 trials, and plotted the average modulation index in Fig. 5. As expected from the monotonic behavior of the individual functions, the outcome were surfaces that approximate a tilted plane within the parameter space explored (indicted by the colour coding in Fig. 5). Here a reduction in attentional modulation due to increased thalamocortical drive could be overridden by alterations in inhibitory drive and intracortical synaptic efficacy, but less so by spike frequency adaptation. From Fig. 5 it is also apparent that, as the level of acetylcholine increases, the parameters of interest can vary within a fair range but still mimic the increases in attentional modulation found experimentally.

While 5% changes in w_{thal} caused a stronger reduction in attentional modulation than a single 5% change in e.g. w_+, a combined change of 5% in w_+, w_{inh} and g_M would outweigh the effect of w_{thal}. This is shown in Fig. 6, where w_+, w_{inh} and g_M are all changed in steps of 5% for every 5% change in w_{thal}. Now, the change in w_{thal} would need to be ∼2–2.5× stronger than changes in the other parameters (in proportional terms) before a violation of the experimental results occurred, and increased attentional modulation reversed to decreased attentional modulation.

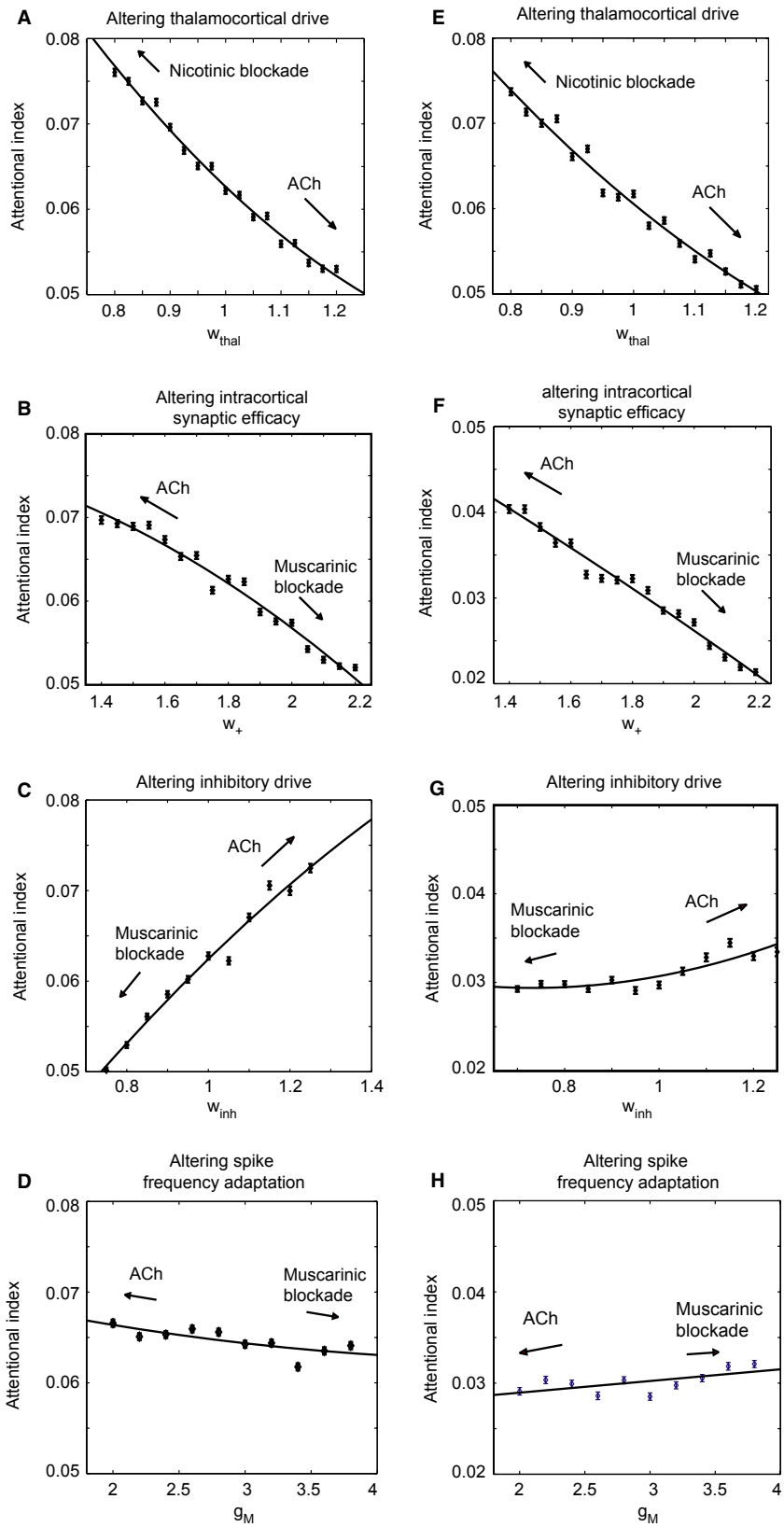

FIG. 4. Attentional modulation as determined by parametrical manipulations of (A and E) the afferent thalamocortical input w_{thal}, (B and F) the excitatory recurrent interactions w_+, (C and G) the inhibitory recurrent interactions w_{inh}, and (D and H) the conductivity of the M-currents g_M. The left column (A–D) shows the effects on a network where feedback connections terminate only on *S1* excitatory neurons. The right column (E–H) shows the effects on a network where feedback connections terminate on *S1* excitatory neurons and on inhibitory neurons. In each subplot, arrows indicate how acetylcholine application or muscarinic or nicotinic blockade would affect the parameter of interest and thus feedback-mediated attentional modulation. The error bars represents the SD over trials, and the black line is a second-order polynomial fitting of the data and has been included to facilitate the visualization of the results.

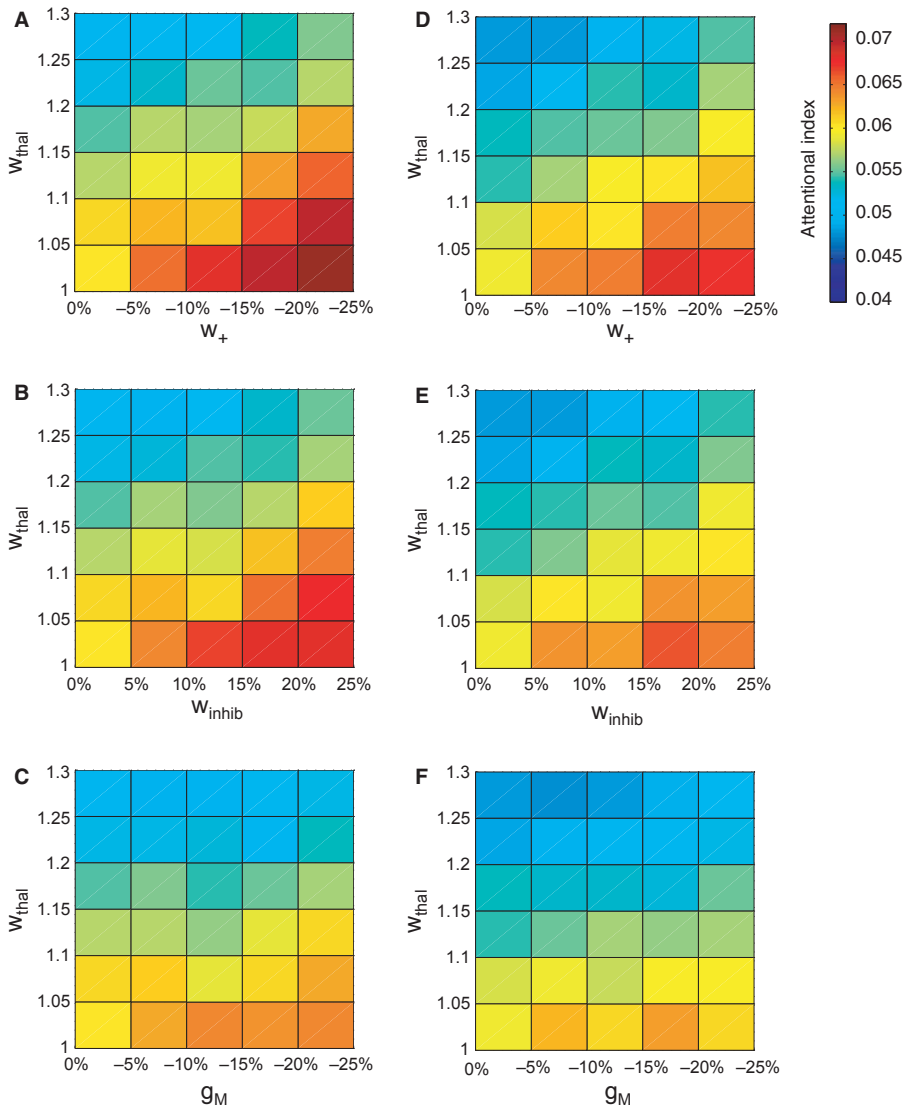

FIG. 5. Attentional modulations as a function of altering the four parameters of interest in steps of 5% from an assumed level of standard cholinergic drive. Increasing cholinergic drive would increase thalamocortical efficacy, which reduces attentional modulation. As this was the only parameter to consistently reduce feedback-mediated attentional modulation when cholinergic drive was raised it is allowed to vary independently in all subplots, and the effects of variation of the other parameters are explored. (A and D) Effect of increasing w_{thal} and decreasing w_+ in steps of 5% on feedback-mediated attention, (A) when feedback terminates exclusively on excitatory neurons and (D) when feedback terminates on excitatory and inhibitory neurons. (B and E) Effect of increasing w_{thal} and increasing w_{inh} in steps of 5% on feedback-mediated attention, (B) when feedback terminates exclusively on excitatory neurons and (E) when feedback terminates on excitatory and inhibitory neurons. (C and F) Effect of increasing w_{thal} and decreasing g_M in steps of 5% on feedback-mediated attention, (C) when feedback terminates exclusively on excitatory neurons and (F) when feedback terminates on excitatory and inhibitory neurons.

Overall, our analyses suggest that acetylcholine influences feedback-mediated attention mainly by reducing the efficacy of the excitatory recurrent connections w_+ and, depending somewhat on where feedback terminates, also by increasing the inhibitory drive w_{inh} within the V1 network.

Discussion

In this paper, we have shown how a theoretical model aids the interpretation of neurophysiological experiments. A number of experiments have delineated the effects of cholinergic neuromodulation on the cortical network (Gil *et al.*, 1997; Hasselmo, 1995; Hasselmo *et al.*, 1997; Hsieh *et al.*, 2000; Kimura, 2000; Sarter *et al.*, 2005; Hasselmo & Giocomo, 2006). However, the relationship between these cholinergic effects and cellular activity within a framework of attention has not been studied systematically. We adopted a computational approach to understand the functional effects of neuromodulation on cortical networks, and how they might promote specific behaviourally relevant functions. We have explored cholinergic manipulations which induce a variety of changes in cortical interactions, and all of these exerted significant influences on feedback-mediated attentional firing rate modulations. As different cholinergic manipulations (agonists, specific antagonists) alter the network interactions and cellular parameters in different ways, they also have a variety of effects on modulation of attention, i.e. some changes resulted in up-regulation while others resulted in down-regulation of the firing rate. The model, constrained by experimental data, helps to disentangle their effects on attentional modulations. Overall our data suggest that high levels of ACh enhance feedback-mediated attentional modulation by reducing

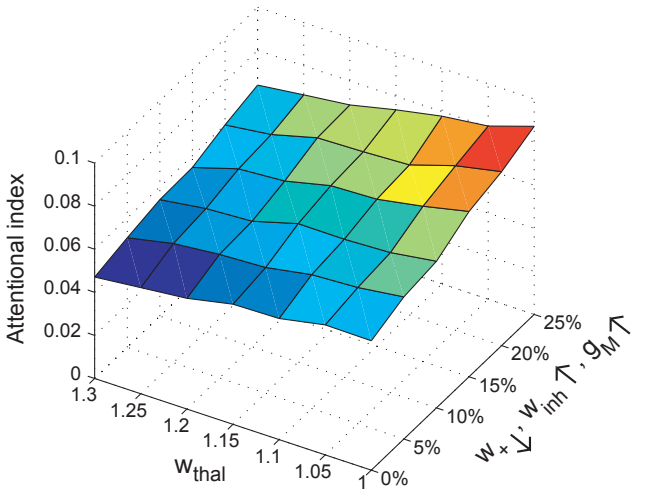

FIG. 6. Attentional modulations as a function of altering all four parameters of interest in steps of 5% (increasing w_{thal}, decreasing w_{+}, increasing w_{inh} and decreasing g_M, from an assumed level of standard cholinergic drive. Here all parameters were varied simultaneously in steps of 5%. The effects of w_{+}, w_{inh}, and g_M (direction of change is indicated by the arrows) outweigh the effects of w_{thal}, and thus attentional modulation increases for every step change performed.

excitatory recurrent interactions, and by increasing the overall inhibitory drive within the network. Blocking the actions of ACh through the muscarinic antagonist scopolamine reduces feedback-mediated attentional modulation by enhancement of excitatory recurrent interactions and by reducing the inhibitory drive within the network.

The effects can be intuitively interpreted as follows: reduced levels of recurrent excitation reduce the overall activity level in a population and, consequently, the attentional bias (the feedback signal) has a proportionally larger effect and results in larger activity differences between the biased and nonbiased state. Thus, a less excited system is much more sensitive to feedback and yields more attentional modulation. A similar effect is caused by the cholinergic modulations of the inhibitory neurons. An increase in inhibition reduces overall drive within the network, and a bias through feedback tips the balance in favour of the biased neurons, i.e. increased inhibitory drive in the presence of bias results in higher attentional modulations.

Reduced intracortical excitation and increased inhibition might decrease intracortical firing, and one could thus suspect that increased ACh should reduce firing levels. While this is regularly reported by *in vitro* studies (e.g. Xiang *et al.*, 1998; Gulledge & Stuart, 2005), we did not see any evidence for reduced firing rates upon ACh application in either anesthetized marmosets (Roberts *et al.*, 2005; Zinke *et al.*, 2006) or awake macaques (Herrero *et al.*, 2008). Conversely we did find overall slightly increased firing rates *in vivo*. This may occur because reduced intracortical excitation also affects the excitatory drive to inhibitory interneurons (see Fig. 3), thereby possibly compensating for the effects. Moreover, there is recurrent inhibition between the inhibitory interneurons (Fig. 3), which would result in a limiting effect of increased inhibition. Finally, acetylcholine reduces spike frequency adaptation and, while this was not a main factor that contributed to attentional modulation in our model, it may be a factor that compensates for possible reductions in firing rate. It is possible that all these factors interact, which might put the network into a state of balanced excitation and inhibition (Ozeki *et al.*, 2009). A network that operates in a state of reduced but balanced excitation and reduced inhibition may still elicit higher firing rates when sensory stimuli are presented, but where the feedback from higher cortical areas may be much more effective in driving attentional modulation. For additional information on how firing rates were affected by our manipulation, see Supporting Information Figs S1-S3. It could in principle also be the case that the ACh drive in our network increases the firing in inhibitory neurons more than the reduction in drive that ensues from inhibiting the excitatory cells, which would violate a state of balanced excitation and inhibition. Whether our network really works in a state of balanced excitation and inhibition will require additional network analyses which are beyond the scope of this paper. Finally, as mentioned at the outset, there are a variety of other mechanisms that are influenced by acetylcholine which were not considered in the model delineated here, but which may also contribute importantly to overall increased firing rates *in vivo*.

There is experimental evidence showing that ACh increases the thalamocortical input to the cortex (Gil *et al.*, 1997; Disney *et al.*, 2007). In principle it may thus be possible that under attention w_{thal} is increased. The reason why we did not selectively increase w_{thal} with attention is that most feedback explicitly avoids layer 4. Strong inter-areal connections that terminate in layer 4 are characteristic of feedforward, not feedback, systems (Felleman and van Essen, 1991). Thus, in order to change w_{thal} with attention, one would need to alter the cholinergic drive on a trial-by-trial basis, depending on whether attention is towards or way from the neurons' receptive fields. Currently it is unclear whether the spatial specificity exists in the cholinergic system to allow for such controlled alterations. Moreover, the paper set out to explicitly model the influence of feedback, given a specific cholinergic drive, not the possible influence of altering cholinergic drive locally on a trial-by-trial basis. We would envisage that the latter could possibly produce attentional modulations that are similar to those seen in the current paper, but future experiments need to determine whether there is an anatomical and physiological basis for such tightly controlled ACh release in sensory areas.

The contribution of increased inhibitory drive to attentional modulation is intriguing. Recent experiments have suggested that putative inhibitory interneurons are more susceptible to attentional modulation than are principal cells (Mitchell *et al.*, 2007; Chen *et al.*, 2008). This has been a puzzling finding, as there is a widely held belief that principal cells transmit the benefits of attentional modulation from area to area, whereby the modulation increases somewhat at each processing stage. In line with the finding that inhibitory neurons show larger attentional modulation, our analysis suggests that inhibitory drive, powered by ACh, exerts a strong control over attention-induced firing rate change. A strong effect on the inhibitory drive in V1 by ACh is expected from anatomical data, as V1 interneurons are the main carriers of muscarinic somatic receptors (Disney & Aoki, 2008). Activation of somatic muscarinic receptors causes cellular depolarization (McCormick & Prince, 1986), and thus excites these cells. Our model did not attempt to determine whether attention increases firing rates more in inhibitory interneurons than in principal cells, as found by Mitchell *et al.* (2007) and Chen *et al.* (2008). Future models will have to incorporate differential cell type-specific receptor distributions to yield an answer to this question.

Another main factor that contributed to enabling feedback-mediated attentional modulation in our model was a reduction in synaptic efficacy of excitatory intracortical synapses (lateral connections). We have deliberately left the efficacy of feedback connections unaltered by acetylcholine because we wanted to explore what happens to the influence of a specific feedback signal when the model network undergoes intra-areal changes that are compatible with those induced by altered cholinergic drive. However, it may be possible that acetylcholine also alters the efficacy of feedback connections.

Feedback connections often terminate in layer 1 (Anderson & Martin, 2006), where the highest density of cholinergic axons and varicosities is also found (Avendano *et al.*, 1996; Mechawar *et al.*, 2000). In mouse visual cortex layer 1, glutamatergic synaptic transmission is increased through nicotinic receptor activation (Lucas-Meunier *et al.*, 2009), and it might be possible that ACh specifically enhances feedback glutamatergic drive. On the other hand it may also be possible that feedback connections affect acetylcholine release in layer 1 (or other layers) rather than the other way round. This would enable a high spatial specificity of the ACh signal. Future experiments will be necessary to determine whether acetylcholine and feedback connections interact, and delineate their exact interaction.

Within the context of this paper we have focused on how acetylcholine contributes to attention-mediated rate modulations, and have deliberately ignored the role of gamma frequency oscillations. This is because attention decreases neuronal synchrony in the gamma frequency range in V1 (Chalk *et al.*, 2010), rather than increasing it as reported for V4 (Fries *et al.*, 2001; Gregoriou *et al.*, 2009; Chalk *et al.*, 2010). While at first this result may seem puzzling, it may not be entirely unexpected. A variety of models have proposed mechanisms of attention-mediated increases in gamma frequency oscillations for V4, including a possible role of ACh in their mediation. At the same time it is well established that cholinergic receptor distributions differ between striate and extrastriate cortex. Modelling shows that attention-mediated increases in neuronal synchrony in the gamma range can occur when adaptation currents in principal cells are reduced, and cholinergic mechanisms have been suggested (Borgers *et al.*, 2005). Alternatively it can be mediated by decreasing the activity in inhibitory interneurons (Buia and Tiesinga, 2006, 2008), thereby releasing pyramidal cells from a 'bath of inhibition' (Borgers *et al.*, 2008). The reduction in inhibitory drive on pyramidal cells might be mediated by cholinergic activation of interneuron–interneuron inhibition (Borgers *et al.*, 2008). Specifically, Borgers *et al.* (2008) suggested that increased gamma with attention may occur because ACh increases the activity in a specific inhibitory cell class (e.g. low threshold spiking or cholecystokinin cells) which then inhibits parvalbumin cells. This inhibition reduces the overall inhibitory drive within the network, allowing it to reach a state in which gamma oscillations are favoured. While this is a possible scenario for extrastriate cortex, anatomical data show that muscarinic receptors in V1 are mostly expressed by parvalbumin cells (Disney *et al.*, 2007) and ACh would thus increase, not reduce, the inhibitory drive in the pyramidal-inhibitory loop. This difference could be one of the reasons why V1 shows the attention-mediated decrease, not increase, in gamma oscillations. However, one prediction of such a scenario is that the overall firing rate would be reduced, not increased, with attention (Borgers *et al.*, 2008), but experimental data show otherwise (see Fig. 2). Future detailed modelling and additional experimental studies may be necessary to provide more insight into the differences between striate and extrastriate attentional effects on oscillatory activity.

Here we have shown that constraining theoretical investigation by experimental results provides insight into possible mechanisms by which neuromodulators and transmitters can affect attentional modulation of firing rates. Our data delineate two main components by which acetylcholine affects attentional modulation. Firstly, it increases sensitivity to an external attentional bias by decreasing the recurrent excitation within the network. Secondly, it increases the inhibitory drive within the network, through its activation of muscarinic receptors on interneurons in V1.

Why would it be computationally advantageous to get acetylcholine involved? From an engineering point of view, one might simply increase the feedback drive to generate the attentional modulation. There are two interlinked arguments which could explain this. The cholinergic system is strongly involved in development (Hohmann & Berger-Sweeney, 1998), plasticity (Miasnikov *et al.*, 2008) and learning (Rokem & Silver, 2011). Attention is equally important for learning (Seitz & Watanabe, 2005), but the focussed attention system that is present in primates (and other mammals), which relies on feedback from 'higher' cortical areas is evolutionary a relatively novel invention, compared to the basal forebrain cholinergic system which is present in fish and amphibians as well (e.g. Sanchez-Camacho *et al.*, 2006). It may thus be the case that the novel cortically controlled attention system is built to interact with the older plasticity system to enable attention-controlled learning. To reiterate a frequently used argument, evolution tinkers with pre-existing systems rather than inventing details *de novo*.

Further insights may be gained into the mechanisms of attention by future studies if additional effects of ACh are taken into account. It may be important to model cell type-specific expression of various receptors, as these expression levels can vary strongly even between areas V1 and V2 (Disney *et al.*, 2006). It would be surprising if these more complex models would not yield additional mechanisms by which ACh can alter attentional modulation. It will also be important to explore in a formal model possibilities as to why attention decreases gamma oscillations in V1 when simultaneously increasing firing rates. However, our data presented here are a first step towards a mechanistic understanding of the action of the neuromodulator ACh and its role in attention. In particular, they show that while feedback biases the attentional signal it may have limited efficacy in the absence of adequate cholinergic drive. Our data suggest that feedback and ACh are both necessary to mediate attentional modulation and promote adequate behaviour.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Firing rates in the presence (blue) and absence of an attention feedback signal (red).

Fig. S2. Network dynamics for the case where the attentional feedback only drives excitatory *S1* neurons.

Fig. S3. Network dynamics for the case where the attentional feedback drives both excitatory *S1* neurons and the inhibitory pool.

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Abbreviations

EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; M, muscarinic (currents); MI, modulation index; *S*1, the selective population of model neurons which was sensitive to the specific visual stimuli used in the experiments; *S*2, the nonselective population of model neurons which grouped all the remaining excitatory neurons not involved in the ongoing tasks.

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