

Attention as Sigma-Pi Controlled ACh-Based Feedback

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Abstract— We analyse experimental data on attention to indicate that any attention feedback control signals to lower order cortical sites will lead to a quadratic sigma-pi form of output in its dependence on the lower-order input and the feedback signal. The manner by which this structure works is shown by a brief simulation. We then discuss how such a structure could arise from the action of diffuse acetylcholine signals from the NBM, especially involving nicotinic receptors. We deduce certain structural regularities which should be expected both at local- and at micro-circuit level, mainly in cortical layer V (the output layer).

I. INTRODUCTION

Attention has been studied extensively in the mammalian brain. Both brain imaging techniques and multi-unit and single cell recordings have been used to advance this knowledge. At the same time, the effect on attention of deficits has led to further insights. More recently elucidation has begun of the manner in which acetylcholine, noradrenaline and possibly dopamine function as essential neuro-modulators in attention. On this broad base of results a general picture has emerged of the attention circuits and microcircuits in the brain.

This picture is not yet clear enough to set up detailed simulations of the various processes and to relate these to the data obtained by neuroscience. In other words the general picture is still only that, a qualitative one, and not yet of quantitative form. The reasons for this are unclear, but may depend on more experiments aimed especially at the critical questions:

- 1) Is the feedback attention control signal (to lower sensory cortices from the parietal control centres) of additive or multiplicative form with respect to input stimuli and feedback signal?
- 2) How is the feedback control specificity with respect to input stimuli obtained from what appears to be a diffuse ACh signal from the NBM (Nucleus Basalis of Meynert)?

It is these two critical questions (chosen for the relevance to our own work out of many possible questions about attention) which we address here.

II. SIGMA-PI ATTENTION FEEDBACK

There are now several experimental results showing that attention functions so as to increase the contrast gain of the psychological response function. The critical results here are results of attention on single cell responses [1], [2]. These were, in particular, modelled in the original paper of Reynolds et al, as well as somewhat more fully in [3]. The basic result is that the response of a neuron, say in V4, to an attended stimulus was shown to be (in terms of mean firing rate neurons):

$$OUT = f(\text{attention amplification} \times \text{input activation}) \quad (1)$$

where f is some sigmoidal response function. Moreover the attention amplification factor in (1) is dependent on some prefrontal goal, as the preferred stimulus. Thus the attention amplification signal has to arise from some top-down signal specifying the goal. Then (1) has the form of a sigma-pi neuron, with the membrane potential depending quadratically on the product of the feedback signal and the input signal. A more complete expression for (1), in standard sigma-pi form, is

$$OUT(i) = f(\sum w_{ijk} x_j x_k) \quad (2)$$

where i denotes the label of lower sensory cortical neuron under consideration, j denotes the label of the attention feedback source, and k denotes the label of the stimulus input being attentionally amplified. This attention amplification has value $w_{ijk} x_j$, so increasing with the strength of the attention feedback.

It is not the case that present single cell data support (1) if the feedback signal is taken to be graded. No experimental data as to how the strength of the attention feedback signal modulates the stimulus strength in (1) is known to us. This is part of the critical data mentioned earlier needed to move the picture of attention towards a quantitative form.

It has been alternately supposed, and used in simulations [4] that attention feedback acts in an additive manner, so that what replaces (1) is:

$$OUT = f(\text{stimulus input} + \text{attention feedback}). \quad (3)$$

It has been claimed that (3) can lead to similar contrast gain attention results as does (1), but it is clear that in the Reynolds et al paradigm [1] that is not possible. Indeed the attention feedback in (3) functions only in a general manner to boost the total activity of a given neuron and not to amplify a given (attended) input against un-amplified distracters.

To see this in more detail, we reconsider the analysis of the Reynolds et al data given in Appendix B of [3], to take account of the possibility that attention has a linear feedback form as in (3). The data were taken from single cells in monkeys who were attending, or not, either to a probe P or a reference stimulus R, shown so as to be in the receptive field of the cell. The important indices SE and SI were defined as

$$\begin{aligned} SE &= P - R \\ SI &= (P + R) - R \end{aligned} \quad (4)$$

where $(P + R)$ denotes the activation of the neuron when both P and R are present. Therefore SE is the difference in response between the probe and reference stimuli and SI is the difference between the response generated by the probe and reference stimuli together and the reference stimulus alone. Data on an ensemble of cells lead to the linear regression formula:

$$SI = \text{constant} \times SE + \text{constant}. \quad (5)$$

This formula was derived analytically in Appendix B of [3], with the value of the regression constant in 5 shown to be $\frac{1}{1+(1/u)}$, where u is the amount of relative attention paid to the reference stimulus, as compared to the probe stimulus.

The data of [1] was shown in [3] to be well fitted by choice of $u = 1$ when no attention is paid to either the reference or probe, $u = 5$ when attention is paid to the reference and $u = 1/5$ when attention is paid to the probe.

When the same analysis is performed with only an additive attention effect as in (3), this can be absorbed by redefinition of the positive reference input, so leading to the result (5), but with no dependence of the regression constant on whether or not attention is being paid to either the reference or probe or to neither of them. This is clearly in contradiction with the data of [1]. The slopes in the attend reference, attend probe and no attend cases were found to be about 0.5, 0.83 and 0.2, values that clearly are very different.

We conclude that this data is in contradiction with the assumption that attention acts purely by a feedback additive bias, as in (3).

Our result can be extended to spiking neurons, in which various models of contrast gain, driven by modulatory inputs, have been suggested [5], [6], [7]. All of these would still give, for an additive attention feedback signal (in which the feedback is independent of what is attended to), that the attend P and attend R slopes of the curve of SI against SE would be

the same; as noted above these slopes are experimentally very different.

III. SIGMA-PI SIMULATION

The use of sigma-pi attention feedback is investigated in a simple model of spatial attention. The model is based upon the dorsal route of visual cortex, parietal areas and the frontal eye field (FEF), regions known to be involved in spatial attention. The structure is shown in Figure 1, each region modelled is composed of an excitatory layer (e) and an inhibitory layer (i), with each layer composed of 14×14 leaky integrate and fire neurons (the numbers of neurons are chosen to be equal rather than 4:1, excitatories to inhibitories, for simplicity in connectivity).

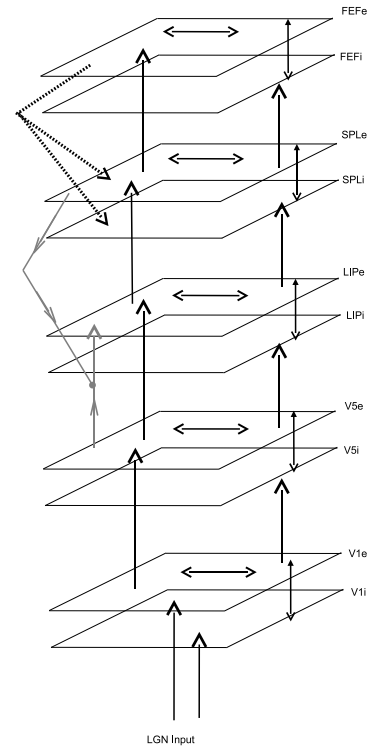


Fig. 1. Structure of the model. Excitatory connections are indicated by open arrow-heads, inhibitory connections by close arrow-heads, sigma-pi connections by grey arrows.

There are lateral excitatory connections within each excitatory group of neurons, with excitatory projections to the related inhibitory nodes. Inhibition then flows back to the excitatory component of the region, to refine the pattern of activation. The flow of activity is, generally, upwards from lateral geniculate nucleus to primary visual cortex (V1), then to V5, up to lateral intra-parietal cortex (LIP), then superior parietal lobe (SPL) and finally FEF. As a spatial input is processed at each subsequent level its representation becomes more focused as it moves up the network. FEF acts as a working memory, holding its processed spatial representation for up to 500ms.

Feedback weights from FEF to SPLe (1:1 connections) and SPLi (1:all) leads to priming of SPL nodes (some sporadic firing may occur).

The sigma-pi weights link SPLe (as feedback controller) and V5e (as input to LIPe) to LIPe, with connectivities being 1:1, and for the sigma-pi weights to exhibit their multiplicative effects SPLe and V5e spikes to LIPe must occur within some time-window (here chosen to be 20ms). With a memory held in FEF of the desired spatial location to attend an input composed of the preferred location and a distracter is presented to the network. These two inputs are processed in the lower levels up to LIP as normal, when activity is now input to SPL the priming from FEF preferentially activates the representation in SPL of the location to be attended rather than the distracter. This speed up in activation of SPL allows the sigma-pi connections to LIPe nodes from SPL and V5 to start working causing a higher firing rate at LIPe nodes representing the location to be attended, the spread of inhibition in LIP over time leads to the destruction in LIPe of most of the representation of the distracter location (Figure 2) and subsequently at higher levels.

IV. THE NEUROCHEMISTRY OF ATTENTION

If we are to understand how attention operates in the brain, we need to know what the underlying neurochemical processes that facilitate attention are. The brain has a number of neuromodulatory chemicals, all of which are possible candidates for use in attention, we will look at these and explain which are the most important.

A. Neuromodulators – which are important?

Of the brain's four primary neuromodulators - acetylcholine (ACh), norepinephrine/noradrenaline, serotonin and dopamine, the most important seem to be ACh and noradrenaline. Serotonin's role in visual attention seems to be limited, while dopamine affects attention [8], but in a manner that is not yet entirely clear.

Noradrenaline's role in attentional processing seems to be that of alerting to a new stimulus, rather than focussing of attention – see [9], for example. The locus coeruleus (the source of cortical noradrenaline) appears to participate in generating a general state of alertness in the brain, rather than allowing concentration on a single stimulus.

From these results, it appears that ACh is the most important neuromodulator for specific attentional focus, a conclusion that is supported by numerous studies of the effects of cholinergic deficits on attention [10], [11]. We will next look at the types of ACh receptor that might be involved.

B. Nicotinic and Muscarinic ACh receptors

There are two types of ACh receptor, muscarinic and nicotinic. Muscarinic receptors have been shown to be capable of modulating glutamatergic response [12], [13]. In the hippocampus, these modulatory effects have shown to be a potential mechanism for sleep state switching [14].

They also have some role in attention – in [15], it is shown that scopolamine (a muscarinic antagonist) adversely affects

attentional processing. Muscarinic receptors do, however, seem to be responsible more for alerting [11], orienting [15] and modulation of visual attribute processing [16]. However, we believe that nicotinic acetylcholine receptors (nAChRs) are the more important for visual attention (based on [11] among others). We will therefore focus on the mechanisms by which nAChRs might direct attention.

C. Mechanisms of nAChR function – a problem with varicosities?

The second question raised in the introduction was as to the mechanism allowing the acetylcholine to achieve the attended stimulus specificity as shown in (1) (or (2)). This is clearly a problem in view of the general diffuse spread of axons from the NBM (the source of cortical ACh) [17], [18], [19]. There have been numerous studies of the distribution of ACh varicosities in the cortex [20], [21]. In general they conclude that, in the rat, only about 15% of such varicosities are synaptic. In the macaque, this number is closer to 45%. This leads to the acceptance of the idea that ACh acts in cortex in a diffuse manner, undergoing volume distribution. However that leads to a clear inability that ACh could thereby support any stimulus or goal specific effects. It would only be able to amplify (or reduce) all input stimuli.

In humans there appears to be a glimmer of hope, in that the proportion of synaptic ACh varicosities is higher, at 67% [22]. These let us consider how such ACh varicosities could function so as to lead to a quadratic sigma-pi form of attention feedback control.

There are several steps we need to take to get to our final point:

- 1) Assume a suitably high proportion of the ACh varicosities are synaptic,
- 2) Nicotinic receptors on cortical neurons, associated with the synaptic varicosities, act in an amplificatory manner on nearby synaptic weights [19].
- 3) Attention feedback control signals axon boutons arrive close to the nicotinic receptors on the cortical neurons, so as to amplify the level of ACh release.

The sigma-pi structure is seen to arise on the basis of the above steps.

Thus we make several predictions about the architecture needed to carry out this construction:

- 1) There should be local apposition of axon boutons from higher areas and ACh varicosities associated with nicotinic receptor units.
- 2) Given that higher-level feedback can go to layer V, the output layer (where there are known to be a relatively high density of ACh varicosities) and that lower area feedforward will go to layer IV then II/III before output layers, we expect to see correlation of activities arriving from LII/IV and from higher areas onto, or nearby to, the ACh synaptic varicosities for a given LV pyramidal cell.

We note that there is support for the effect of nAChRs on several nearby synaptic sites, as reported in [23] in the case

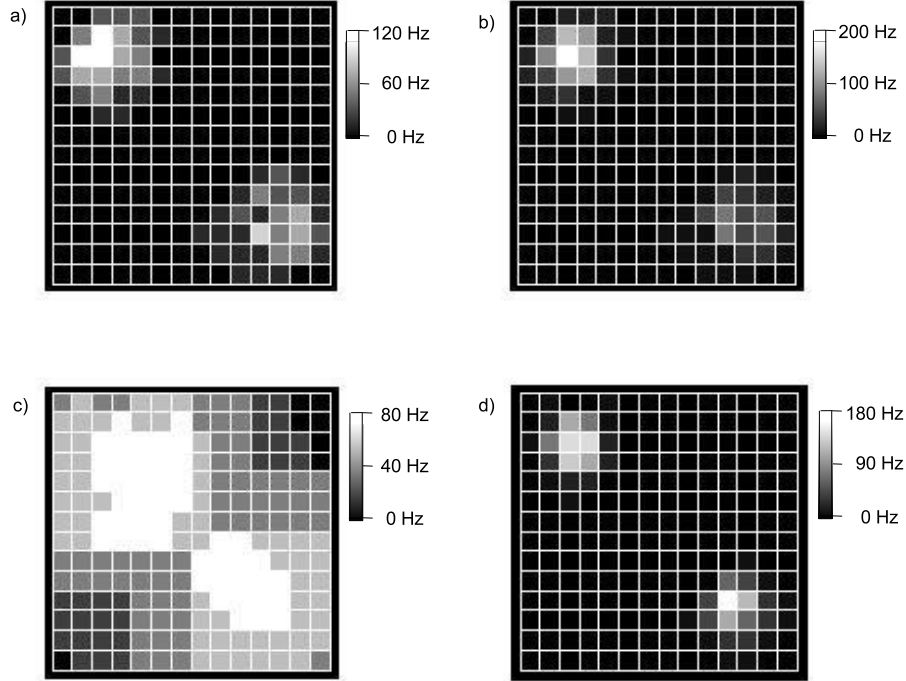


Fig. 2. Development of activity in LIPe neurons a) and b) have sigma-pi weights, c) and d) show the response of the system without sigma-pi weights. Picture a) shows average firing rates of neurons in the first 50ms of 2 location presentation, where the location top-left has been held in FEF working memory. Picture b) indicates the firing rates for the same 2 inputs 100ms later (50 ms time-window). Pictures c) and d) show the development of the firing rates in LIPe nodes without sigma-pi connections, same time periods as a) and b), respectively. There is a greater spread of activity in c) as against a), though the maximum firing rate is lower in c) than a), these effects are a result of the sigma-pi weights causing a higher firing rate (a) which leads to a stronger inhibition reducing the initial representation of locations.

of interneurons in cortex. Generation of GABA currents was shown to occur in interneurons in slices of human cortex, due to the presence of nAChRs. It was suggested there that there is important control of inhibition, say by use of disinhibitory circuits, as in fig 8 of [23]. Such disinhibition may be a crucial component of the overall attention control circuitry. Moreover the amplification of transmitter release by nearby nAChRs is well documented in [24], in [19] and in [25].

The resulting model is expected to have a sigma pi structure of a product form:

$$w_{i,j,k} = w_j w'_k \quad (6)$$

where w'_k is the strength of the connection of the feedback from the k th higher-order attention control neuron to the i th neuron, and w_j that for the input from the j th lower level neuron. This is a specific form which can, we assume, ultimately be tested.

Finally learning of the product form (6) can be expected to be through separate learning of the separate factors in the product term on the right. Thus the total learning rule will have the form:

$$\Delta w_{i,j,k} = OUT_i [OUT_j w'_k + OUT_k w_j] \quad (7)$$

Thus whilst we have made more specific the sigma-pi weights structure, as in (7) and (6), this is still very conjectural, and needs strong experimental support

D. Modulation of glutamatergic input

For ACh to act by contrast gain on excitatory input, it must affect synaptic transmission. Glutamate is the brain's primary excitatory neurotransmitter. Its action at a synapse involves binding to NMDA (N-methyl-D-aspartate) or AMPA (α -amino-3-hydroxy-5-methylisoxazolepropionate) receptors. These receptors cause opening of ion channels through which ions can flow to alter the neuron's membrane potential.

A possible mechanism by which ACh could act at synapses would be by increase of the proportion of ion channels opened by each quantity of glutamate. This would have the effect of amplifying the effects of glutamatergic stimulation.

We can simulate this process, to demonstrate its effects. We use a leaky integrate-and-fire neuron, the membrane potential of which obeys the equation:

$$C \frac{dV}{dt} = g_{leak}(V - V_{leak}) + I_{NMDA} \quad (8)$$

where C is the neuron's capacitance, g_{leak} the leak conductance of the membrane, V_{leak} the neuron's resting potential and I_{NMDA} is a current arising from glutamate activated NMDA

receptors. This model is a simplified version of that used in [26].

The NMDA current depends on two kinetic variables, x and s which we calculate as:

$$\frac{dx}{dy} = \phi(\alpha_x \sum_j \delta(t - t_j) - x/\tau_x) \quad (9)$$

where the sum, j , is over pre-synaptic spike times (representing glutamate arriving from a pre-synaptic neuron). s is then described by:

$$\frac{ds}{dt} = \phi(\alpha_s x(1 - s) - s/\tau_s) \quad (10)$$

such that s , which represents the fraction of open NMDA channels, varies between 0 and 1 (all channels closed and all channels open, respectively). α_s , τ_s and ϕ are constants. The NMDA current is then calculated as:

$$I_{NMDA} = g_{NMDA} s \frac{(V_m - V_E)}{1 + [Mg^{2+}]e^{\frac{-0.062V_m}{3.57}}} \quad (11)$$

where g_{NMDA} is the conductance of ions flowing through these channels. The exponential term represents the effect of a magnesium block on the calcium channels. $[Mg^{2+}]$ is the concentration of magnesium ions around the extracellular end of the ion channel (and assumed to be constant).

We model the effects of ACh, by including a dependency of the constant α_s on the ACh concentration:

$$\alpha_s = \alpha_{s,base}(1 + k|ACh|) \quad (12)$$

where k and $\alpha_{s,base}$ are constants and $|ACh|$ is the local ACh concentration. This models a process by which ACh causes a greater proportion of ion channels to be opened by NMDAR (NMDA receptor) activation.

Simulating the effects of this dependency, we arrive at Figure 3. In 3A, the neuron responds to a periodic glutamatergic input by producing spikes at a rate of 10Hz. When the neuron is also subject to a cholinergic input, in 3B, its activity increases, raising its firing rate to 20Hz. The cholinergic input has no effect on the neuron without glutamatergic stimulation, however. In 3C where the neuron is subject to a purely cholinergic input, it is not activated at all.

This demonstrates a potential neurophysiological mechanism by which ACh can cause gain of glutamatergic input. The model is simple, and would benefit from further expansion and development in accordance with existing technical data on cholinergic modulation of glutamatergic synaptic transmission.

V. CONCLUSIONS

To summarise we have:

- 1) Shown the need for attention feedback control as having a sigma-pi structure.
- 2) Shown how such a feedback, guided by working memory in FEF, is efficient in removing distracters for SPL sigma-pi feedback to LIP related to VR input.

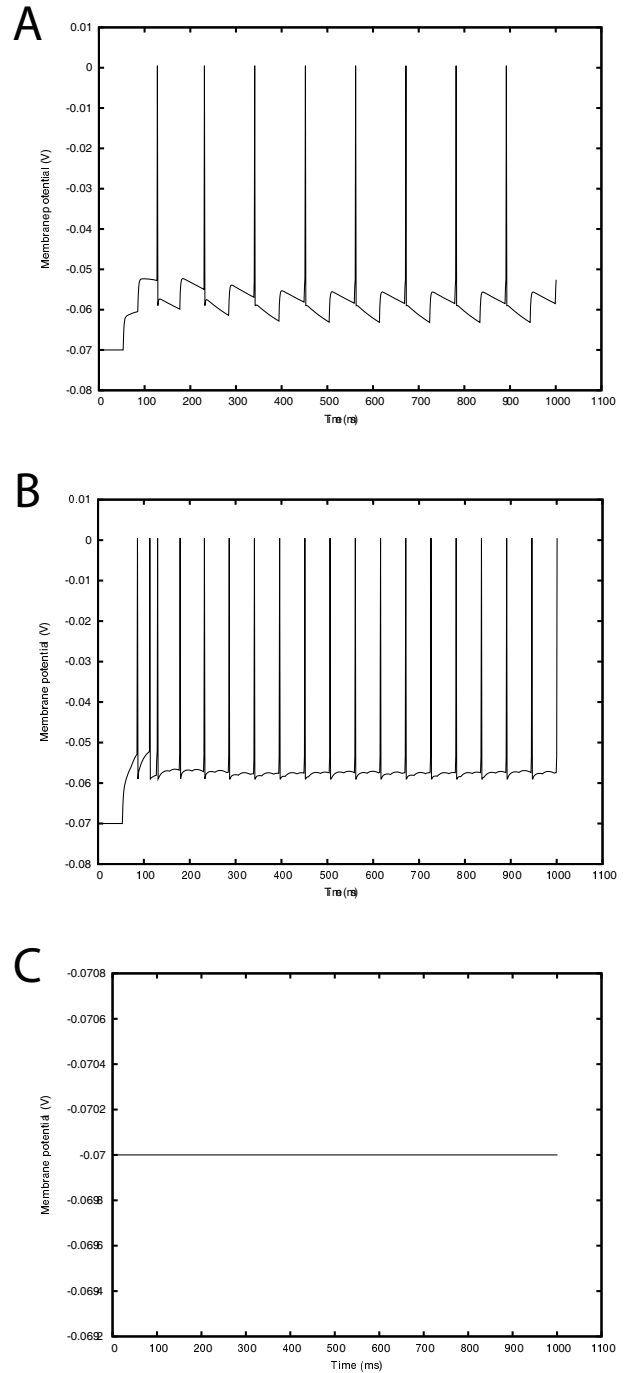


Fig. 3. Effects of ACh on neuron membrane potential and firing rate. In **A**, the neuron is driven by a periodic glutamatergic input which produces a resultant firing rate of approximately 10Hz. In **B**, the neuron also receives cholinergic input which increases the net firing rate (via modulation of the neuron's NMDA channels) to 20Hz. Without glutamate, however, the ACh has no direct affect - **C** shows the neuron's response to a purely cholinergic input.

- 3) Suggested a possible microstructure to obtain such a sigma-pi feedback from an otherwise diffuse ACh flow into cortex, in terms of synaptic nAChRs on cortical neurons, with conjoint feedback axon endings form

higher areas.

- 4) Proposed a simple mechanism as to how there can be amplification of transmitters by nAChR activation and subsequent Ca ion inflow.

The above mechanisms are still very conjectural. What is needed is primate studies on the ultrastructure of synaptic nAChR varicosities in cortex, as well as detailed in vitro or in vivo single cell studies, extending that of [23] to pyramidal cells.

VI. APPENDIX

A. Glossary of abbreviations used in the paper

ACh	Acetylcholine
NBM	Nucleus Basalis of Meynert
FEF	Frontal Eye Field
LIP	Lateral Interparietal Cortex
SPLi/e	Superior Parietal Lobe interior/exterior
nAChR	Nicotinic Acetylcholine Receptor
SE	Difference in cell response between total response to probe and reference and reference alone
SI	Difference in cell response between probe and reference stimuli

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