A New Interpretation of Thalamocortical Circuitry

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Almost all the information that is needed to specify thalamocortical and neocortical wiring derives from patterned electrical activity induced by the environment. Wiring accuracy must be limited by the anatomical specificity of the cascade of events triggered by neural activity and culminating in synaptogenesis. We present a simple model of learning in the presence of plasticity errors. One way to achieve learning specificity is to build better synapses. We discuss an alternative, circuit-based, approach that only allows plasticity at connections that support highly selective correlations. This circuit resembles some of the more puzzling aspects of thalmocorticothalamic circuitry.

1. INTRODUCTION

Almost all the information that reaches the neocortex arrives via the thalamus, which to a first approximation acts as a simple relay. Since the simplest, most efficient relay would be an uninterrupted axon, why does the thalamus exist at all? The unknown functions of the thalamus must be rather general, because its basic anatomy and physiology is universal throughout the various nuclei. It seems unlikely that this universal circuitry is used differently in each nucleus to do specialised processing appropriate to the particular type of information being relayed by that nucleus (visual, somatosensory, auditory, motor, hippocampal etc). This universality has become even clearer with the recent realisation that much (in primates, most) of the relayed information arises from layer 5 of neocortex itself, rather than from subcortical sources (Sherman & Guillery,1996).

The universal core circuits of thalamus include massive feedback from layer 6 of the cortical region to which a thalamic region projects, side projections to layer 6 of the main relay input to middle cortical layers, and relay cell feedforward excitation to and feedback inhibition from reticular nucleus. All these circuits are roughly topographic, although in no case is the detailed pattern of the connections understood (Sherman & Guillery, 2001).

Many aspects of thalamic physiology also seem universal. Some of these (and their anatomical correlates) reflect basic relay function. Thus a particular incoming “driver” axon (which can originate subcortically or from layer 5 of neocortex) typically makes numerous powerful synapses on the proximal dendrites of a relay cell, such that an incoming spike is likely to trigger an outgoing spike with a very short, fixed delay. Each relay cell receives only one such major input, though it may also receive a few subsidiary synapses from other “driver” axons. However, other universal features seem inexplicable in a simple relay scenario. For example, relay cells all have 2 firing modes, “tonic” and “burst”, both of which carry out effective (though slightly different) relay functions (Guido et al, 1995).

A popular view is that the universal function of thalamus is "gating" (Steriade & McCarley, 1990). In its simplest form, this asserts that the thalamus selects which information is sent on to cortex. In one extreme form, the gate would be closed throughout thalamus during sleep, and the rhythmic bursting of relay cells would be a sort of busy signal or screensaver. In the awake thalamus, bursting would also be a "no signal" mode, but could be selective for individual nuclei, or even individual relay cells, and might correspond to an attentional "spotlight" (Crick, 1984). However, the discovery that in the awake state bursting is irregular and time locked to driving input (Swadlow & Gusev, 2001) is difficult to square with "no-signal" hypothesis. Instead it seems likely that both burst and tonic modes are relay modes, and that the firing mode instructs cortex how to handle the incoming information, rather than fundamentally changing that information.

We present here a speculative account of some of the universal features of thalamocortical circuitry and physiology, based on the idea that complex circuits should be built using accurate synaptic learning.

2. CONNECTIONISM

Clearly whatever thalamus does, it is intimately related to whatever the neocortex does. Although neocortex does a vast range of different things, a suitable starting point is that it probably uses rather basic "connectionist" principles. These principles are (1) cortical neurones integrate their synaptic inputs and provide outputs to other neurones (or more formally, neurones compute weighted sums of their inputs), and (2) changes in activity-dependent synaptic strength program these neuronal computations using purely local rules signals (for example, Hebbian rules in unsupervised learning), perhaps together with global feedback. The ways in which these connectionist principles actually work out in terms of circuits, synaptic weights, coding strategies etc may vary greatly from region to region, but these important details are unlikely to explain universal aspects of thalamocortical circuitry.

Connectionist principles have to be embodied in real neurones and synapses, which have limitations of accuracy and speed. A reasonable starting guess might be that the thalamus exists to minimise the impact of these limitations, to which very elaborate networks like the neocortex might be particularly sensitive. One obvious possibility is that real biological inputs and outputs, encoded as spike trains, contain noise caused by imprecise spike timing, ultimately traceable to the small sizes of neural components and finite ion channel numbers. It has been proposed, for example, that intracortical recurrent circuitry can minimise such noise, by a sort of spatial averaging mechanism (Deneve et al 1999). Some currents ideas about the thalamus (Sillito et al 1994, Dong & Atick, 1995) could fit into this category.

Another aspect of "biological connectionism" that has hitherto been largely ignored centers on the second half of the connectionist paradigm - local activity-dependent weight setting. Two obvious biological limitations that are usually ignored in connectionist

modelling are (1) biological networks are very sparsely connected (because neural numbers are huge and neural wires are expensive), and (2) because synaptic learning is a physical event, using small numbers of molecules, it cannot be anatomically completely precise.

The traditional view of the first problem is that appropriate sparse connectivity is "precomputed" by Darwinian gene-based evolution, and hard-wired by suitable marker molecules (netrins, ephrins etc). Activity-dependent synaptic learning is then used to set appropriate strengths of existing connections. An example of this is the use of "arbour functions" in models of visual cortex development (Miller,1990;1994). Particularly striking evidence for such hardwiring comes from the olfactory system (Wang et al, 1998) where individual wiring is achieved using thousands of special purpose markers. However, in a way this beautiful example actually shows the weakness of the hardwiring approach as a general strategy, because these markers monopolise a significant fraction of the entire genome. The strategy works here only because these markers, which are the odorant receptor molecules themselves, are available "gratis" for the secondary task of hooking up olfactory neurones to the appropriate glomeruli in olfactory bulb. It would be impossible to coarsely wire the neocortex using such a costly, precomputed marker approach.

There is a second even more powerful argument against extensive cortical hardwiring. Only those features of the environment that persist over thousands of generations can be exploited by gene-based evolution. Prewiring eliminates most of the advantages of flexible learning that are thought to be a neocortical hallmark. Finally, there is considerable experimental evidence against such hardwiring (Sur & Leamey 2001).

It is widely suspected that sprouting provides a bridge between genetically-specified hardwiring and activity-dependent learning at fixed complete connections (Miller 1990). Thus sprouting from existing connections could provide trial new connections which are then tested by activity-dependent synapse adjustment (Willshaw & von der Malsburg, 1979; Fraser & Perkel, 1990). Unfortunately this approach has not been very extensively tested. It is commonly assumed that sprouting provides a "free lunch", in that it allows new configurations to be tested, without seriously degrading the quality of the final set of connections and weights (which could be more speedily attained with unbiological complete connectivity). However, there is some evidence that this may not be so (Elliott et al, 1996).

The second biological limitation of synaptic learning is that it may be anatomically imprecise, in that not only the connection across which there is correlated activity may strengthen, but nearby inactive connections may be affected also. There is a good deal of evidence that this occurs in hippocampus (Bonhoeffer et al, 1994; Engert & Bonhoeffer, 1997; Schumann & Madison, 1994) and in neocortex (Kossel et al 1990). It has been argued that spines exist to compartmentalise the calcium signals that are the immediate trigger for synapse strengthening (Koch & Zador, 1993), which suggests that minimisation of anatomical learning inaccuracy has been of enormous importance in the vertebrate nervous system, and it has been widely assumed that such compartmentation is

complete. However, this hope is unrealistic because there are concomitant opposing pressures to miniaturise synapses, which makes anatomical specificity harder to achieve.

A final limitation that biological realism imposes on connectionism concerns the dynamic range of synaptic learning. Typical models require a wide range of possible synaptic weights, which can be implemented biologically in 2 different ways: varying the strengths of individual synapses ("physiology") and varying synapse numbers ("anatomy"). There is as yet no good experimental evidence as to how long term weight changes are distributed between these 2 routes, although there is some evidence that as time progresses physiological changes are converted to anatomical changes (Colicos et al 2001). The most efficient arrangement would probably be to make the initial change at the level of existing synapses (increasing transmitter release, phosphorylating existing receptors, recruiting additional receptors), and then (perhaps if immediately subsequent activity does not countermand these temporary changes) convert these changes *pari passu* to a change in the number of synapses. "*Pari passu*" refers to the fact that the switch from physiological substrate to anatomical substrate should preserve the "strength" of the connection, a parity which raises some interesting cell biological questions.

If synaptic strengthening is anatomically imprecise, and involves creation of new synapses, these new synapses may not always form at the connection across which triggering activity occurred, and may even involve the creation of new synapses. This could be regarded as an activity-dependent "sprouting" mechanism, and could be either presynaptic or postsynaptic, or both. Such "accidental" new synapses could provide a solution to the problem of finding the best set of connections in a very sparsely connected network such as neocortex. However, such anatomical errors could also severely degrade network performance. We propose that thalamus could set the balance between flexibility and accuracy during neocortical learning. In the next section, we explore these ideas more quantitatively.

3. A MODEL OF SYNAPTIC ERROR

As a first step, we constructed a very simple model of synaptic learning that allows a more quantitative discussion of these issues. We consider a single presynaptic neurone (such as a lateral geniculate relay cell) that can connect to a set of postsynaptic neurones (such as the set of layer 4 cells in striate cortex that are the potential targets of lgn cells). The aim is to accurately connect the relay cell to a subset of these cortical cells using activity-dependent mechanisms. In our model, the various layer 4 cells do not influence one another, so each set of connections can be considered independently. The postsynaptic neurones are "linear", so their output V_i ("activity") is simply given by the

weighted input activity $w_i V_{pre}$, where w_i is the strength of the connection to the *i*th postsynaptic cell:

$V_i = w_i V_{pre}$ ……. Eq 1

An important feature of the model is that when a connection strengthens it does so in a digital manner, by adding new synapses. Because synaptic strengthening occurs in an all or none manner (Petersen et al ,1998), addition of synapses should occur probabalistically. Except when errors occur, the new synapses added as a result of coincident activity across a connection should have the same "connectivity" as the synapses comprising the original connection, and the only reasonable way to accomplish this is for a new "daughter" synapse to be closely associated with an existing "parent" synapse, either because the original synapse "divides" (Carlin & Siekevitz, 1983; Toni et al, 1999; Luscher et al, 2000; but see Fiala et al, 2002) or because of *de novo* formation of a bouton/spine pair very close to the original synapse, the new bouton belonging to the same axon as the parent bouton, and the new spine belonging to the same dendrite as the parent bouton (Colicos et al, 2001). Either mechanism seems compatible with the expectation that the biochemical triggers for activity-dependent synaptogenesis act locally near or at the initiating synapses. In either case the fundamental mechanism is one of synaptic "replication", in which the connectivity of the new synapse is specified by and triggered at an existing synapse.

In the model we used a standard Hebb rule, according to which the change in strength of a connection due to coincident activity is proportional to the product of the presynaptic and postsynaptic firing rates (k_i is a, possibly connection-specific, learning rate).

$dw_i/dt = k_i V_{pre} V_i$ ..... Eq 2

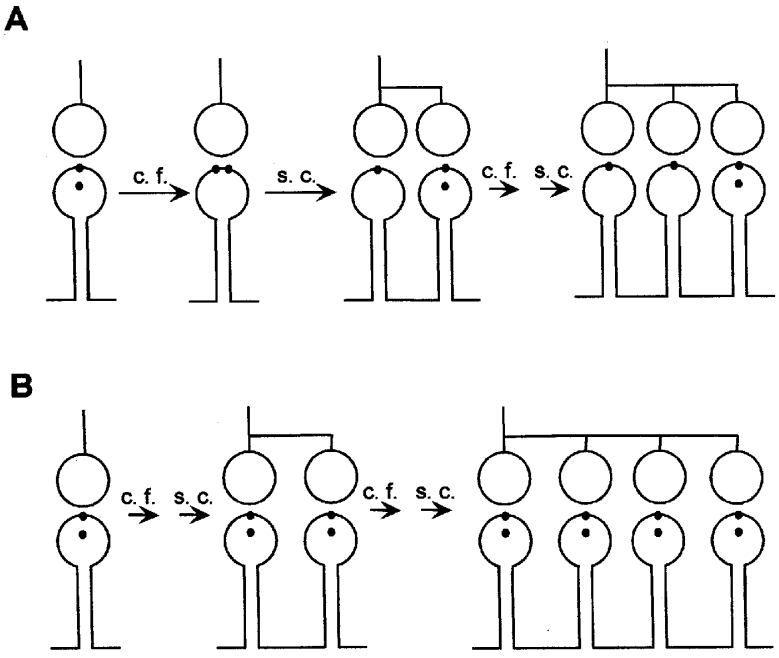

Fig 1. Asymmetrical and symmetrical synaptogenesis following correlated firing ("cf") across a connection. In this figure the new synapses preserve the connectivity of the original synapse, though this does not necessarily imply physical splitting. A group of AMPA receptors is shown a black dot. AMPA receptors located in the membrane of the spine head are electrophysiologically functional and endow a synapse with its "strength". AMPA receptors located in the spine head interior are electrophysiologically silent, but constitute a reserve pool which endows a synapse with plasticity. In part A, correlated firing across the connection, initially comprised of one synapse, leads to physiological strengthening (insertion of a group of AMPARs). The strengthened synapse is no longer plastic (the actual mechanism could be different from depletion of the reserve, which is used here as an iconic representation of plasticity). This is followed by structural changes ("sc") that convert the temporary 2-strength synapse to two 1-strength synapses, only one of which however regains its plasticity. If the same amount of correlated firing occurs again, the same strengthening of the connection occurs (as in a conventional Hebb's rule). In part B, both the orginal and the new, correlation-induced, synapses are plastic, so a second episode of correlated firing leads to a larger increase in synaptic strength (in contradiction to the usual quantitative formulation of Hebb's rule). Thus in both parts "strength replication" and "connectivity replication" are symmetrical, but only in part B is "plasticity replication" symmetrical. If the new synapses do not have the connectivity of the original synapses, the result would be a "synaptic mutation".

How is this rule to be interpreted at the level of single synapses? If the probability that each existing synapse gives rise to a new synapse depends simply on the coincident activity, then the effective gain of the Hebb rule over the whole connection would increase as more synapses are added, and Eq 1 would not be obeyed (see Fig 1B). To use a traditional Hebb rule in a framework of individual synapses (rather than the abstract "synaptic weight" of traditional models), appears to imply that the probability that coincident activity causes synapse replication depends inversely on the number of

synapses comprising a connection – a decidedly "nonlocal" and rather implausible requirement. Instead, we suggest that when replication occurs, either the existing or the new synapse be "implastic" (Fig 1A). This would allow the Hebb rule to operate locally at individual synapses (which is where the machinery appears to be located), while preserving the Hebb rule quantitively over the whole connection. Thus coincident activity would promote "replication" of the connectivity and strength of existing synapses, but not their plasticity. The rather anticlimactic result of this discussion is that we retain a conventional Hebbian learning rule, though expressed in terms of synaptic number rather than weight.

Combining Eqs 1 and 2, we obtain

$dw_i/dt = \phi_i w_i$ …… Eq 3

where $\phi_i = k_i V_{pre}^2$. The parameter ϕ_i plays a rule rather similar to "fitness" in evolution models. Straight Hebbian learning leads to unlimited synaptic growth, which is biologically unrealistic, especially when expressed in terms of synapse number. Most models introduce a "normalisation" process at this point, for example constraining the total number of synapses made by the presynaptic neurone to be constant. There are various ways to biologically implement such normalisation, such as competition for growth factors, inclusion of a non-Hebbian forgetting term, or use of a time dependent learning rule, but in our simulations we used a brute force normalisation, dividing the weights by a factor that kept their sum constant. Thus activity merely triggered synapse rearrangement between the various target cells.

So far this model exhibits very simple behavior (von der Malsburg & Willshaw, 1980). Connections with high ϕ_i values grow at the expense of low ϕ_i connections, and eventually all but the "fittest" connections disconnect. The Hebbian rule is able to detect and amplify small biasses and generate a completely precise set of final connections. However, these final connections are irreversible, since there is no way to create new connections.

We now introduce synaptic error, by assuming there is some low probability E that a new synapse created by conjoint neural firing appears not at the connection across which conjoint activity occurred, but at an adjacent connection (even if that "connection" was nonexistent, with no synapses). The learning rule becomes

$dw_i/dt = (1-E)\,\phi_i w_i + E(\phi_{i-1} w_{i-1} + \phi_{i+1} w_{i+1})/2$ ……..Eq 4

(This could also be regarded as a rule incorporating coactivity-dependent sprouting; the vital point is that it provides for the creation of new connections).

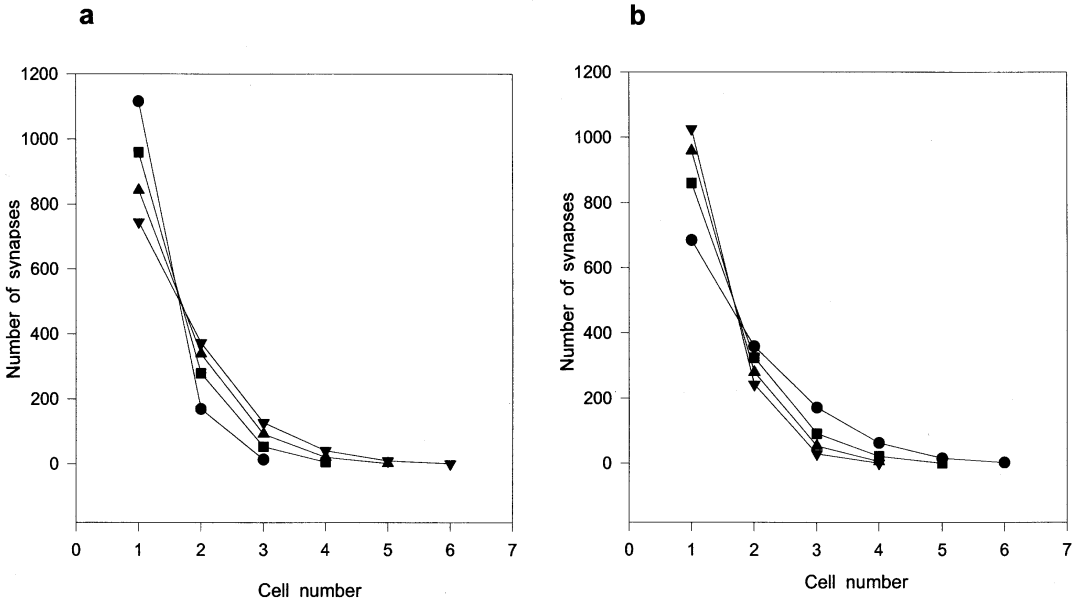

Fig 2. Simulations of the steady state distribution of synapses on target neurones for various error rates (left) or fitnesses (right). In each case the left connection was the fittest ($\phi = \phi_m$), and there were 13 neurones and 1300 synapses. Connections on neurones 2-13 had uniform low fitness ϕ_p. The average number of synapses on each neurone achieved at equilibrium is shown for various values of error rate E and fitness ratio ϕ_m/ϕ_p (No synapses were formed on neurones 7-13, which are not shown). In all cases synapses are most numerous on the high fitness neurone, but as error rates increase (left graph) or fitness ratios decrease (right graph) synapses become more spread out. Values of E used in part **a** were 0.1 (circles), 0.2 (squares), 0.3 (inverted triangles) and 0.4 (triangles), with $\phi_m/\phi_p = 1.4$ throughout. Values of ϕ_m/ϕ_p used in part **b** were 1.11 (circles), 1.25 (squares), 1.42 (inverted triangles), 1.66 (triangles), with $E = 0.2$ throughout.

We simulated the behavior of this model numerically, using a row of 13 target neurones and a probabalistic version of Eq 4 for the formation of individual synapses. We assigned a high value, ϕ_m , for the neurone at the left end of the row, and a uniform low value ϕ_p over the remainder of the row. We found that eventually a steady state distribution of synapses was attained, with (as expected) most of the synapses located near the preferred neurone, but a considerable tail of synapses straggling away from it (Fig 2). This steady tail arises because synapses leak from the high fitness neurone at a rate which exactly compensates for the excess production there. Also as expected, we found that increasing the error rate or decreasing the fitness ratio ϕ_m/ϕ_p led to a broader tail of synapses (Fig 2). As expected, zero error leads to completely specific connections.

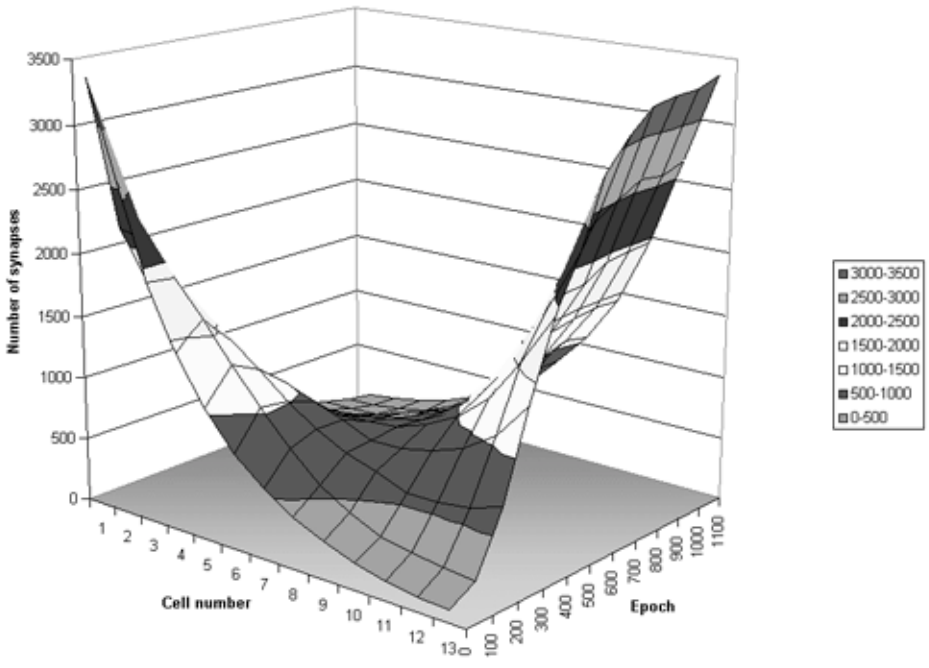

Fig 3. Migration of synapses following a mirror reversal of fitness. Initially synapses were equilibrated with the leftmost connection (on cell 1) being 5% fitter than the others. This resulted in the zero epoch profile, with most of the synapses on cell 1, but with some spread across the entire set of target cells. The rightmost connection (on cell 13) was then made 5% fitter than the others, and the resulting profiles plotted for successive epochs (after attainment of equilibrium and then binning results for 20 consecutive epochs to reduce noise). The total number of synapses was 13,000 and the error rate 0.25.

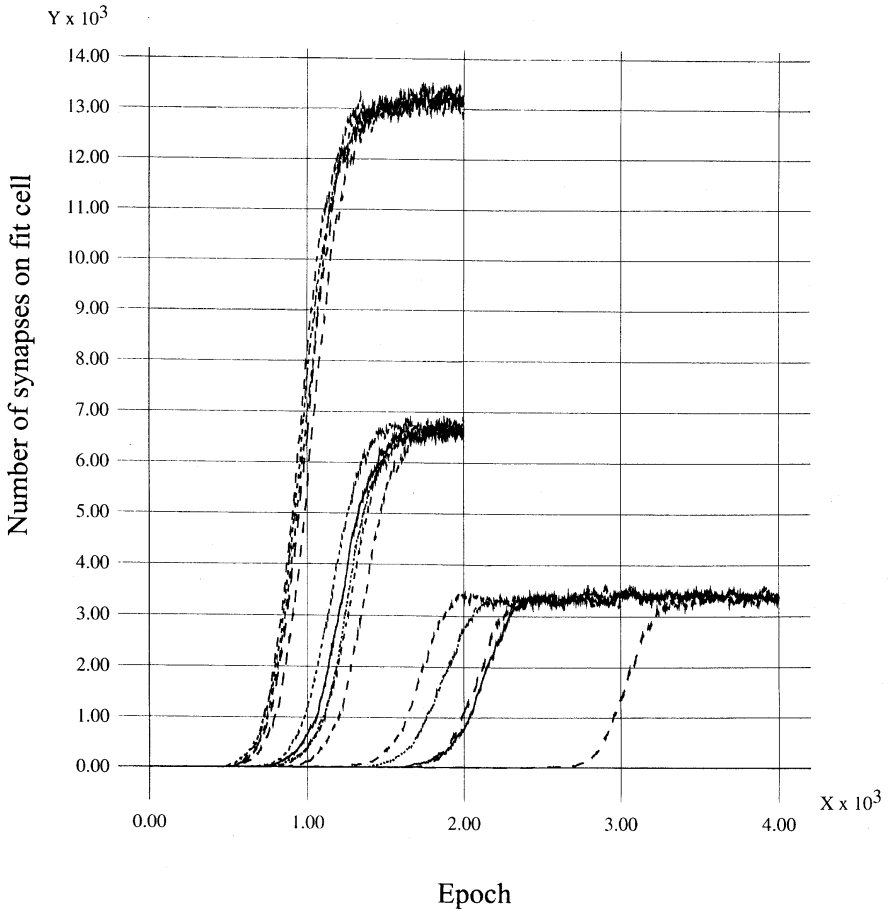

Fig 4. Kinetics of appearance of synapses at the fittest connection, on the rightmost neurone (cell 13). All synapses were initially placed on the leftmost neurone. The number of synapses on the right neurone was plotted at successive epochs. The total numbers of synapses M were 26,000 (left 5 runs), 13,000 (middle 5 runs) or 6,500 (right 5 runs). Note that there is a variable delay before the formation of the first synapse on the fittest neurone, followed by rapid increase in the connection strength. However, because for the parameter values used ($E = 0.1$, $\phi_m/\phi_p = 1.05$) the length constant is quite high, the fittest neurone only gains about half of the total number of synapses.

We also examined the transient behavior of the model. Fig 3 shows the initial steady distribution of synapses generated when the leftmost neurone was fittest, and the subsequent migration of synapses when the rightmost neurone instead became the fittest. The initial trail of synapses acts as a seed for the growth of the rightmost connection. In Fig 4, all the synapses were initially placed on the leftmost neurone, and then allowed to migrate to the fitter, rightmost neurone. The figure shows the number of synapses accumulating on this target neurone. There is an initial, rather variable delay before the first synapse reaches the target, which then rapidly flourishes. As expected, this delay grows smaller the larger the total number of synapses.

The model can be analysed straightforwardly in the continuum limit (large numbers of synapses and neurones). In the above equations *w* becomes a synapse density at the point *x* on a continuous neuronal line, and Eq 4 becomes

$$\partial w/\partial t = (\phi - \langle\phi\rangle)\, w + 0.5\, \phi\, E\, \partial^2 w/\partial x^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq 5}$$

(The average fitness $\langle\phi\rangle$ is introduced to enforce weight normalisation, see von der Malsburg & Willshaw, 1980). Although Eq 5 is nonlinear, in the steady state $\langle\phi\rangle$ attains some constant value, leading to an ordinary second order differential equation, whose solution in the particular case of a high fitness mesa surrounded by a low fitness plateau is, over the low fitness plateau,

$$w_p = C \exp -x/\lambda_p + D \exp x/\lambda_p \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq 6}$$

where $\lambda_p^2 = E\, \phi_p /2\, (\langle\phi\rangle - \phi_p)$ and *C* and *D* are constants. For short mesas and long plateaus (the conditions of our simulations), the second term on the RHS can be neglected, and the decay outside the mesa is exponential, as observed. The space constant λ_p is given by

$$(2\lambda_p + n)/\, n\lambda_p^2 = 2(\phi_m/\, \phi_p - 1)/E \qquad \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq 7}$$

where *n* is the number of neurones in the mesa. We found that the distributions in our simulations were close to exponential, with space constants described by Eq. 7 (Fig 5).

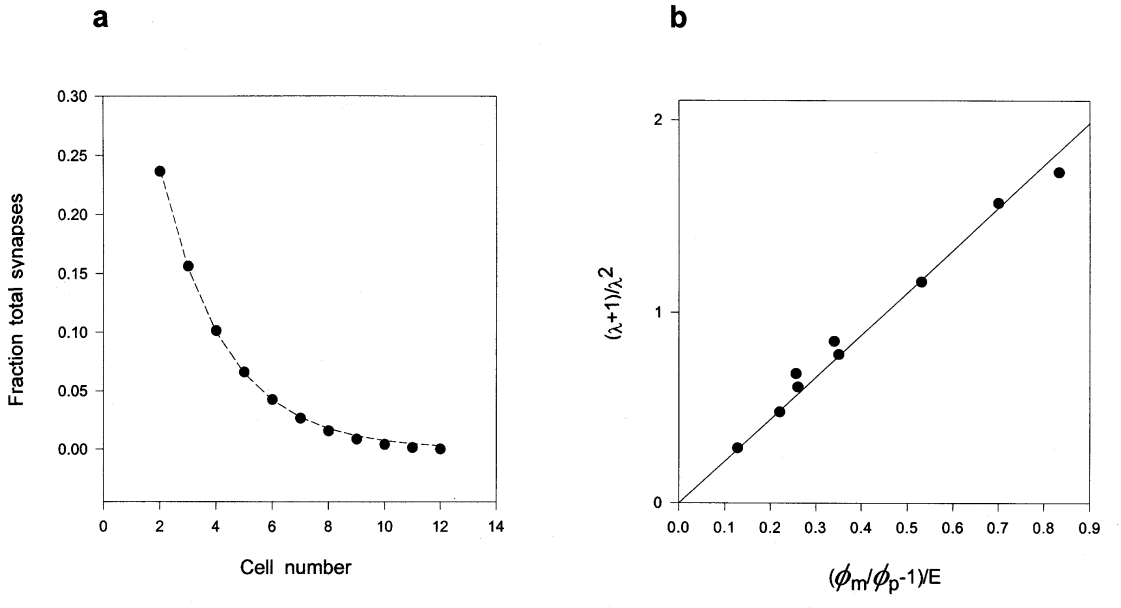

Fig 5. Comparison of simulation results (points) to theory (lines). Part **a** shows the fraction of the total number of synapses (13,000) that form at less fit connections (i.e. the plateau region) compared to an exponential curve of length constant λ= 2.45 neurones). E = 0.2; ϕ_m/ϕ_p = 1.05. Cell 13 received no

synapses and was omitted. Part **b** shows the reciprocal effects of relative fitness and error rate. Each point was obtained for a different combination of ϕ_m/ϕ_p and E from data like that shown in part **a.** The linear regression through the origin has a slope of 2.2, compared to the predicted slope 2.0 (see Eq.7). Because in the simulation the fit neurone was at the end of the line, while in the analysis it is the middle, n=2).

This is a highly simplified model of synaptic rearrangement, probably the simplest that exhibits selective wiring, but it clearly shows an intuitively plausible phenomenon which is probably common to more elaborate models, that incorporation of anatomical error into a learning rule produces a blurring of connections away from the precise pattern attained in the absence of error. Furthermore, it illustrates quantitatively (Eq 7) the expectation that the extent of blurring is greater when error rates are high or when targetting signals are weakest. We regard the mutual interdependence of the factors that promote blurring (i.e. error) and those that enhance specificity (selective neural activity) of capital importance, because it means that correlational mechanism (such as Hebb's rule) cannot build circuits of unlimited precision. Furthermore, even very low synaptic error rates could be of great significance in preventing the self-organisation of large networks such as neocortex because correlations in the real world are likely to be weak and near the limits of detectability (a tiger in the grass).

4. A SLIGHTLY MORE REALISTIC MODEL OF SYNAPTIC LEARNING

Although the above model shows the basic phenomena, it is rather unrealistic, because it neglects interactions between different inputs (other than the normalisation process), and does not really specify the origins of the postulated fitness differences. To some extent this can be remedied by flipping the model, so that a row of presynaptic cells projects onto a single, linear postsynaptic cell. We can now ask what stable set of weights emerges if the input neurones are subjected to a given series of patterns. This model (without synaptic error) is essentially the prototype of all connectionist unsupervised learning models (Diamantaras & Kung 1996). Because the Hebb rule detects correlations, in a fully connected error-free network the weight vector gradually aligns with the leading eigenvector of the covariance matrix of the set of patterns, also known as the principal component. Each pattern "pulls" the weight vector towards itself, and an equilibrium is attained when all these little pulls balance out. If the set of patterns is visualised as a cluster of points in high-dimensional space, then the principal component is the least squares line through these points, the direction along which the variability of the points is maximal. The postsynaptic neurone evolves to act as an ideal statistical filter, since its output in response to any particular pattern is the projection of that pattern on the principal component.

If an unvarnished Hebb rule is used, although the weight vector aligns with the principal component, the weights themselves grow without bound. This could be remedied by constraining the sum of the weights to be constant (as in the previous section). However, to allow for both positive and negative activities and weights, it is usual to normalise the sum of the squares of the weights. This can be done using a purely local rule, involving

an additional “forgetting” term given by the product of the square of the postsynaptic activity and the weight (Oja 1982).

We are currently investigating how introducing learning errors modifies the behavior of this single neurone principle component analyser. We find that the weight vector now stabilises to a new direction that is intermediate between the principle component and the direction corresponding to a uniform weight distribution, so that the neurone no longer acts as a statistically optimal filter. The extent of degradation of the filter depends both on the error rate *E* and on the structure of the covariance matrix.

This behavior can be seen particularly clearly in the limiting case where the patterns are uncorrelated, corresponding to a cloud of points whose main axis is aligned with one of the input coordinates. This coordinate represents the input neurone whose activity over the set of patterns has maximal variance. If the patterns are uncorrelated, then the optimum arrangement is for the postsynaptic neurone to be connected exclusively to the “most interesting” input neurone, the one whose variance is maximal. In this particular case, since the patterns are uncorrelated, the evolution of any particular synaptic weight does not depend on the evolution of the other weights, but only on the variance of the relevent input neurone. For uncorrelated patterns the model becomes identical with that in the previous section, with the variances replacing the fitnesses. In the simplest case where the variance at one input neurone is high, and the variance for all the other input neurones is low, the main weight will be on the correct neurone, but it will not be exclusive, there being an exponential tail of weight distribution onto “nearby” neurones. Thus learning errors lead to a suboptimal filter.

Of course it is unlikely that neurones in the visual system, or anywhere else, act as principal component filters, primarily because such a representation is suited only to the simplest type of Gausssian pattern statistics. Nevertheless, something like the core concept, statistically optimal representation, is probably at play in the neocortex , and it is likely that in all cases anatomical learning errors will impose limitations on the self-organisation of neural networks in response to structured inputs. In the next section we consider how the impact of such errors can be minimised.

5. LIVING WITH ERROR

One obvious way to minimise the impact of learning errors is to lower the error rate, by optimising the machinery of synaptic plasticity. Perhaps the most obvious possible way for synaptic weight adjustment to be anatomically imprecise would be diffusion of second messengers involved in the plasticity cascade from active to inactive synapses. Of these messengers calcium is the best understood and probably the most important, since calcium influx through NMDA receptors seems to be crucial for Hebbian learning. Consistent with the idea that activity-dependent learning should be synapse-specific, spines (which are found wherever vertebrate learning occurs) seem to exist to compartmentalise these calcium signals, by a combination of physical barriers and biochemical machinery (Koch & Zador, 1993).

However, achieving the goal of complete synaptic independence is incompatible with the equally desireable goal of maximising synapse numbers (since ultimately the amount of useful information that can be stored in a neural network depends both on the numbers of synapses and the precision with which their strengths can be independently set). For example, increasing the distances between synapses decreases both crosstalk and numbers. Over the open times of NMDA receptors (~100 msec) even well buffered calcium diffusion ($D \sim 0.01$ $msec^{-1}$ um^{-2}) can span typical intersynaptic distances. The problem is compounded by the requirement that synapses be not only well separated but also small, since this means that rather small numbers of calcium ions must reliably trigger synapse modification.

It is therefore not surprising that recent experimental tests have shown that the synapse specificity of long term potentiation (ltp) can break down quite dramatically (Engert & Bonhoeffer, 1997; Schumann & Madison, 1994). In these experiments one common feature was that the stimulation protocols used to generate ltp were rather drastic, typically involving hundreds of spikes or long maintained depolarisations, precisely the circumstances in which calcium diffusion will be favoured. It seems likely that under more natural conditions, involving rather precise timing of pre- and postsynaptic spikes, and very brief and localised calcium signals, the specificity of synaptic strengthening or weakening will be much greater, but presumably not perfect.

So how can the brain live with ineluctable learning errors? The problem is that, because of the positive feedback inherent in the Hebb rule (which is what makes it so useful), errors can propagate and prevent useful learning, especially when the statistical regularities that guide learning are relatively weak. Ultimately the useful size of a biological neural network must be limited by the accuracy with which the individual "bits" that constitute its "programme" can be written, and this limitation is likely to be particularly severe in a vast network like neocortex which deals with relatively subtle statistical regularities (such as finding principles in masses of neuroscientific data).

More specifically, how can a single lgn relay axon be correctly wired to a handful of neurones out of the hundred million or so in the primate striate cortex, using the statistical correlations that are generated either by intrinsic prenatal activity (such as retinal waves) or postnatal visual experience? Roughly speaking this wiring feat is accomplished because the firing of the incoming axon is more highly correlated, on average, with the firing of the "correct" handful of cells than with the incorrect myriad of other potential targets, although it might also be aided by biochemical cues. However, we have seen in the previous section that if learning is anatomically imprecise, connections will also be formed onto "neighbours" of the correct cells, and these incorrect connections will abound to an extent that depends inversely on how much more the axon's firing is correlated with "correct cells" than with the "incorrect" cells. If the selective correlations that guide wiring are strong, then wiring can be accurate even though the learning rule is anatomically imprecise (see Eq 7). If these correlations are internally generated (for example, by retinal waves) then they could in principle be sufficiently selective that

precise wiring could still be achieved, but if they are generated by interaction with the real world, this cannot be guaranteed, and self-organisation may fail.

It could be argued that although imprecise wiring is inevitable, its flexibility advantage (arising because currently incorrect connections may be useful in the future) always outweighs its drawbacks (poor performance). We suspect however that since errors are inevitable there will always be adequate flexibility, and that the main learning task is to ensure that residual errors do not prevent useful learning.

We therefore suggest the following formulation of the neocortical learning problem. Given that a particular set of "correct" connections has been established as a result of past selective correlations, how can we guarantee that these connections will remain correct if (a) they remain plastic and (b) the correlations are not guaranteed to remain selective? The difficulty is of course that if the network continues to learn, less selective correlations can allow errors to persist, leading to incorrect wiring.

Formulating the problem in this way immediately suggests a solution. If the survival of errors depends on the selectivity of correlations across currently connected neurones compared to the correlations across incipient connections, then a measurement of these correlations (across current and incipient connections) could be used to control learning at current connections. In particular, if the ratio of the correlations across current and incipient connections exceeds some critical value (which will depend on the error rate, and the number of synapses comprising a connection), learning could be switched off entirely, guaranteeing that error will not occur. In this context, an "incipient connection" is defined as one that could be immediately formed as a result of an anatomical error in strengthening of an existing connection and subsequent synaptogenesis of an existing connection. (Of course, further errors could result from strengthening of newly formed "erroneous" connections; the gradual propagation of these errors away from the original "correct" connections underlies the insidiousness of the error problem, but this is avoided if the initial error is prevented).

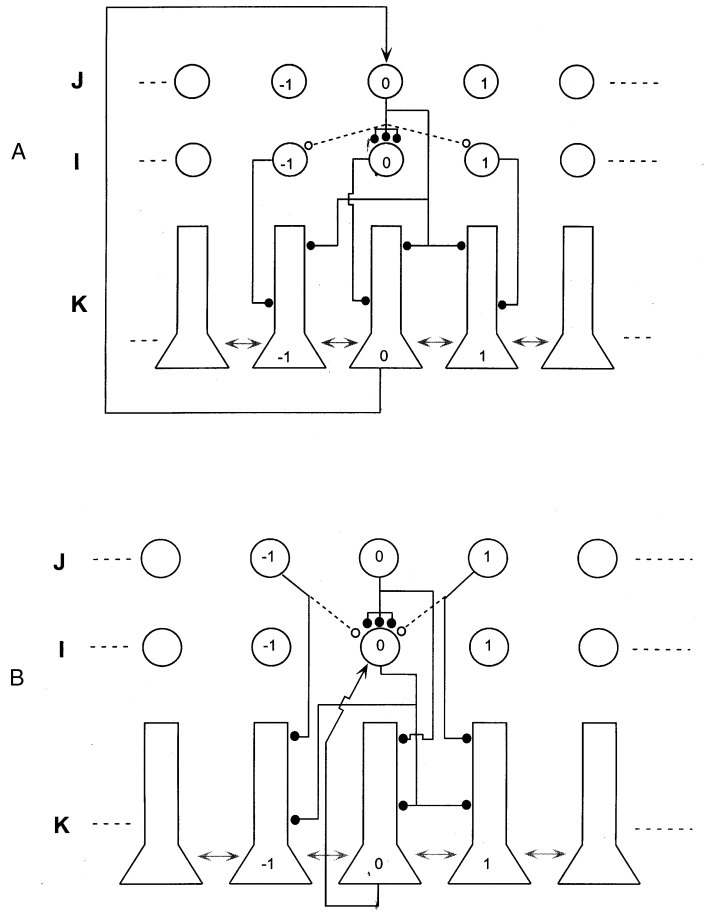

Fig 6. Circuits for error avoidance. In both parts the middle neurone in the top row (J_0) has formed a selective connection (small solid dots) on the centre neurone of the middle row (I_0), as a result of selective correlations in the firing of these 2 neurones. If this connection undergoes further strengthening as a result of correlated firing, the added synapses could (with very low probability) be formed on the neighbors of I_0 (or, more exactly, on neurones whose dendrites are neighbours of the existing connection). These possible "presynaptic error" synapses or "presynaptic mutations", which are incipient connections, are shown as dotted lines and small open circles in part A. If these errors are to propagate they must be supported by adequate correlations in the firing of the J_0-I_{-1} or J_0-I_1 pairs, compared to $J_0 - I_0$ correlations. These correlations are measured by K neurones in the bottom layer. If propagation of errors is unlikely, K_0 fires, presynaptically enabling the plasticity of the current connection made by J_0.

Part B illustrates an alternative "postsynaptic" scenario, in which strengthening of the J_0-I_0 connection could cause inorrect synapses to form from neighbours of J_0 (or, more precisely, from axon branches which neighbour the existing connection). In this case the correlations that must be measured by K-neurones are slightly different, and if their selectivity is favourable, plasticity of the current connection should be enabled postsynaptically. In real networks, each J cell can make several connections on I cells, and each I cell can receive several inputs from J cells. In these cases the relevent correlations, measured by K cells, are the average correlation across the current connections, compared to the average correlation across incipient connections (see Fig 7)

The circuitry that is required to implement this solution is shown in Fig. 6. Presynaptic neurones are labelled J, postsynaptic neurones are labelled I, and neurones which detect correlations are labelled K. Actually, 2 different though related circuits are needed, corresponding to 2 different types of synaptic learning error. If an anatomical error is made in creating a synapse at an existing connection, the erroneous synapse could be made either between the correct presynaptic neurone and an incorrect postsynaptic neurone (dubbed a "presynaptic error" because the initial correct change is presumably initiated presynaptically, but triggers the selection of an incorrect postsynaptic target which happens to be available nearby), or between the correct postsynaptic neurone and an incorrect presynaptic neurone (a "postsynaptic error"). (Error rates are assumed to be sufficiently low that the probability of a double error is negligible). In Fig. 6A the set of incorrect "neighbors" onto which errors can be made is depicted, for convenience, as the neurones whose cell bodies are "neighbors" of the cell bodies of the correct neurones. However, the actual set of neurones is presumably determined instead by the anatomical disposition of the terminals of the presynaptic neurones and the dendrites of the postsynaptic neurones; difficulties with this assignment are discussed below.

In the case of "presynaptic" errors, it would be necessary to measure the correlations between the currently connected neurones, and also the correlations between the currently connected presynaptic neurone and the postsynaptic neurones to which it could become connected if an error occurs Fig 6A). These correlations would be measured using a special type of coincidence-detecting "K" neurone, shown using a different symbol from the conventional pre- and postsynaptic J and I neurones. Excitation of K- neurones would be caused by a pair of spikes, one in a presynaptic neurone and one in a postsynaptic neurone, with a suitable timing delay corresponding to the paired spikes which cause the strengthening of the existing connection. K-excitation by a correlated spike pair would also reflect any time dependence of the strength change at the J-I connection triggered by that spike pair. One possible way to accomplish this would be to use similar NMDA receptors to trigger strength changes in J-I connections or excitation of K neurones, but selective innervation of distal and proximal dendrites of K cells (as sketched in Fig 6) could also be employed.

The next step is to compare the excitation of K cells corresponding to current connections with excitation of K cells corresponding to incipient connections. If this relative excitation is strong enough, it must somehow enable the plasticity of the current connection, secure in the knowledge that if this connection strengthens, added synapses will be either correctly placed, or will be inadequately supported by weak correlations. An obvious way to do this would be for the "current" K cell to be inhibited (via an interneurone) by the "incipient" K cells, illustrated in Fig 6 by short horizontal arrows. Thus firing of the current K cell (denoted K_0 in Fig 6) would signal that the present input is well correlated with the firing of the currently connected output, compared to the correlation with the firing of the "neighbors" of the current output, and this firing should therefore enable the plasticity of the current connections (only one shown in Fig 6). Although at first sight it might seem logical to lead the axon of this K cell to synapse at or near the current J-I connections, this would be quite complicated to wire up. It would be much simpler to lead the axon to the cell body of the appropriate J neurone, and to

multiplex onto the spike train emitted by that J cell an additional command, which would automatically enable the plasticity of any connection that J neurone makes onto I neurones. If the average rate of the spikes of the J neurone was used to convey the information about the input, then it would be natural to use a second order statistical parameter such as spike clustering to convey the plasticity-control signal; in the simplest case, a "tonic" firing mode could be used to enable plasticity and a "burst" firing mode could be used to disenable it. Thus the J cell associated with a current connection would continuously monitor the selectivity of the waxing and waning correlations across that connection (just as the strengthening of that connection would itself depend on the flux of the absolute correlations across it), only allowing learning under favorable conditions. (Of course, the I cells would under all circumstances *process* the impinging J-spikes).

Fig 6A illustrates the principle, but it is highly oversimplified. Not only might a given J cell connect to several I cells, but also each I cell could get input from several J cells. Indeed, part of the reason that the firing of the neighbouring I cells I_{-1} and I_1 are to some extent correlated with the firing of J_0 is that they get input from J cells whose firing is correlated with the firing of J_0 (for example because of patterned visual input). These correlations have in the past been insufficient to cause direct wiring to J_0, even though the occurrence of errors tends to promote such wiring. All the other I cells also have their plasticity controlled by suitable K cells, which can be imagined as additional K sublayers not shown in the figure. At first sight it might seem that if there are *n* I-neurones, and each I neurone has *m* neighbours, a total of *nm* K cells would be needed. However, insofar as each J cell innervates several I cells, all these I cells constitute a "current connection", and a single K cell could compute the average correlation between that J cell and its I –targets. Likewise, a single K cell could also compute the average correlation between a J cell and all the neighbors of its current I-targets. (In these average correlations, a K cell would be excited by paired spikes originating in any of its J or I inputs).

What modifications to Fig 6 should be made to allow for the fact that several J cells can converge on a single I cell? For example, in the cat striate cortex several lgn relay neurones converge onto single layer 4 cells, endowing these neurones with their characteristic receptive field properties (Reid & Alonso, 1995; see Fig 7). Presumably this arrangement exists because in the past the activity of these particular relay neurones were highly correlated with the activity of this particular layer 4 target cell (Miller 1994). One way to maintain the specificity of these connections even if present visual experience is less structured than in the past would be to enforce a strong "critical period" outside which plasticity is turned off, but this would make the system inflexible. Instead, the approach advocated here is that plasticity should merely be temporarily disabled, on a connection by connection basis, whenever the correlations that initially wired the connections wane. In this case the output of the K cell that corresponds to the I cell receiving the convergent J-input should be led back to the all the appropriate J cells, and enable their plasticity (Fig 7). (Of course, this has the disadvantage that some of these J cells also make synapses on other I cells, and the plasticity of these connections will also be spuriously enabled. However, by definition, these J cells also make synapses on other I cells, and the K-partners of these I cells will not be firing, limiting the enablement;

plasticity would be controlled in a “distributed” manner just like regular neural computation).

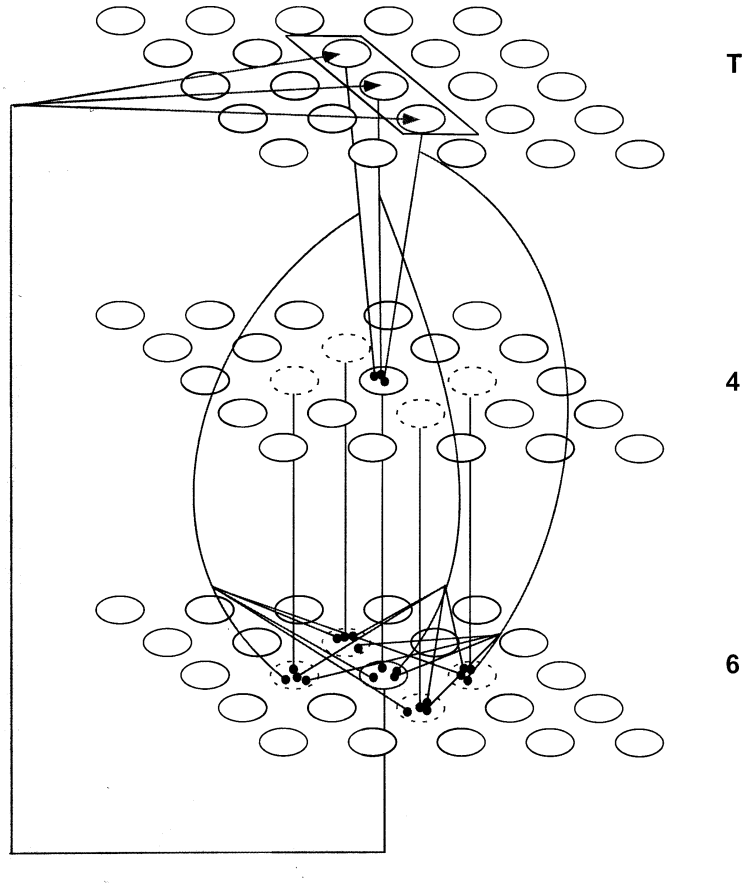

Fig 7. A more realistic version of Fig. 6A, based on the lateral geniculate nucleus (T) projection to striate cortex (layers 4, 6). In this figure the J cells are shown explicitly as thalamic relay cells (T) , the I cells as cortical layer 4 cells (4), and the K cells as cortical layer 6. The corticothalamic feedback connections (arrows) terminate on the distal dendrites of relay cells, where they can activate metabotropic glutamate receptors, which depolarise relay cells and shift them from burst (“implastic”) to tonic (“plastic”) mode. Several relay cells converge on a given layer 4 cell, in this case 3 relay cells responding to a a bar of light or darkness on retina innervating a single “simple” layer 4 cell. This simple cell in turn innervates, via a fixed connection, the soma of its corresponding layer 6 partner, which also receives, on its distal apical dendrite, input from branches of the relay cell axons that innervate the layer 4 simple cell. For simplicity the extended electrotonic structure of layer 6 cells, sketched in Fig. 6, is not shown here. The central layer 6 cell would, by virtue of either of these 2 types of input, itself be simple. (Complex layer 6 cells also occur, but these would correspond to the K-cells shown in Fig. 6B). Note that the activation of the layer 6 cells would depend, in this scheme, on the conjunction of action potentials in its input cells. The firing of the central layer 6 cell then depends on a comparison of its own activation with those of its neighbors (shown as dotted circles), which receive their proximal inputs from the *neighbors* of the layer 4 cell (also shown dotted). Note also that the central layer 6 cell feeds back to all the thalamic relay cells that innervate its layer 4 partner. Although these postulated connections and properties are consistent with the known anatomy and physiology of thalamic and cortical cells, they go slightly beyond it. However, the circuitry shown here, and in Fig. 6, can easily be established by 2 types of offline calibration signals applied in alternation while either the T-6 or 6-T connections are selectively plastic

Fig 6B shows the rather similar machinery that would be required to control "postsynaptic errors." In this case a synaptic strengthening error would involve formation of a connection between a new spine originating at dendrites involved in the current connection, and a bouton forming on an axon terminal that is near to the axon making the original connection. These neighboring axons would form synapses onto K neurones that compute correlations across "incipient" connections (K_{-1} and K_1 in Fig 6B), which would in turn inhibit the "current" K cell K_0, which detects the correlation between the neurones contributing to the current connection. In this case the output of K_0 would be used to control the plasticity of the current connection postsynaptically.

6. COMPARISON WITH THALAMOCORTICAL CIRCUITRY AND FUNCTION

Both Fig 6A and Fig 6B are reminiscent of some of the universal features of thalamocortical wiring. In particular, Callaway (1998) has pointed out that in primate striate cortex layer 6 neurones receive a copy of the input to layer 4 cells (via collaterals of relay cells) and of the outputs of these cells (via descending branches; see also Tarczy-Hornoch et al 1999). In the present scheme, this would arise because layer 6 neurones are essentially evaluating the hypothesis that the spikes fired by layer 4 cells are "caused by" spikes in the relay cells to which they are connected. They also evaluate the alternative hypothesis that some of these layer 4 cells spikes are "caused" by relay cells to which they are not currently connected, but could easily become connected. The definition of "causation" that layer 6 cells use is simply appropriate temporal contiguity. The relative strength of these 2 hypotheses is then used to decide whether to allow the existing connections to be modified by the ongoing neural activity. The reason why plasticity is rationed in this way is because it is a double-edged weapon – it allows refinement of the existing set of weights, but at the potential cost of forming inappropriate connections.

Is there any evidence that layer 6 cells do compute such "correlation selectivity" signals? In cat striate cortex, layer 6 cells fall into 2 major physiological groups, "simple" cells and "complex" cells e.g. Hirsch et al, 1998). The majority of those layer 6 cells that project back to the LGN appear to be simple (Grieve & Sillito, 1995). These cells seem to have similar response properties to the 'simple" and "complex" cells in the overlying cortical column. Simple cells in layers 4 and 6 could have identical receptive fields either because they receive identical afferents, or because the layer 6 cell is driven by the layer 4 cell, but in either case the relevent connections would have to be quite strong. Since the connections are weak, it is more plausible that a layer 6 cell mimicks a layer 4 cell because it receives both sets of input, which reinforce each other, as shown in Figs 6 and 7. But although neurones elsewhere in the brain act as coincidence detectors (Agmon-Snir et al 1998), there is so far no direct evidence for this in layer 6.

The schemes shown in Figs 6 and 7 suggest that a layer 6 cell's projection back to thalamus should innervate the relay cells that drive the layer 4 cell that contributes to that layer 6 cell's receptive field properties. A rather similar wiring arrangement has been postulated on quite different grounds by Sillito et al (1994), for which they have obtained

some evidence. However, the detailed pattern of the connections to and from layer 6 cells is still unknown. There is no evidence that individual spikes or bursts of spikes in relay cells are more or less likely to generate ltp or ltd at thalamocortical synapses, as postulated above.

7. WIRING UP THE ERROR CONTAINMENT CIRCUITRY

Although the above account concentrates on the issue of maintaining appropriate connections in the presence of noisy input and synaptic learning errors, the postulated circuitry cannot prevent error entirely. Most of the errors that do still occur will impair the efficiency with which neural circuits process information, but occasionally a new connection will be useful, especially if environmental changes allow it to support a high level of correlated firing. In these circumstances feedforward circuits could actually rewire, requiring an adjustment of the error-prevention circuitry. These changes are illustrated in Fig 8. The left part of the Figure shows the initial connections. If cell J_0, which (as a result of a previous high degree of correlation) is currently wired to cell I_0, accidentally makes a synapse on cell I_1, activity patterns might change such that the new connection replaces the old connection (as shown in the right part of the figure). The K cell connections that "guarded" the original J_0-I_0 connection are no longer appropriate for guarding the new connection. In particular, the connections shown as dotted in the left part of the figure must be broken, and the connections shown as dashed in the right part must be created. This could be done if the circuit is taken "offline" so it is no longer exposed to the patterned activity that caused the initial J-I rewiring, and is instead subjected to certain internally generated "calibration signals". While offline, the J-I synapses would, by the action of a suitable neuromodulator, be rendered implastic, and unable to respond to the calibration signals. Conversely, the connections to and from the K cells would be rendered plastic (they would be fixed when online). In particular, the required new J_0-K_2 connection could be created if cell J_0 fires selectively and powerfully so that it causes I_1 to fire. The conjoint firing of J_0 and I_1 would then cause K_1 to fire, strengthening the J_0-K_1 connection. Errors in the strengthening of this connection would then create the desired J_0- K_2 connection. The old dotted J_0-K_{-1} connection is neither supported by correlated firing nor the beneficiary of errors, so it will disappear. The feedback connections from K to J would then be modified in a second phase of offline learning, via the correlated firing of J_0 and K_1. In both cases the crucial neighborhood relations underlying the circuitry are established by exploiting error, since a "neighbour" is defined as a cell onto or from which errant synapse form.

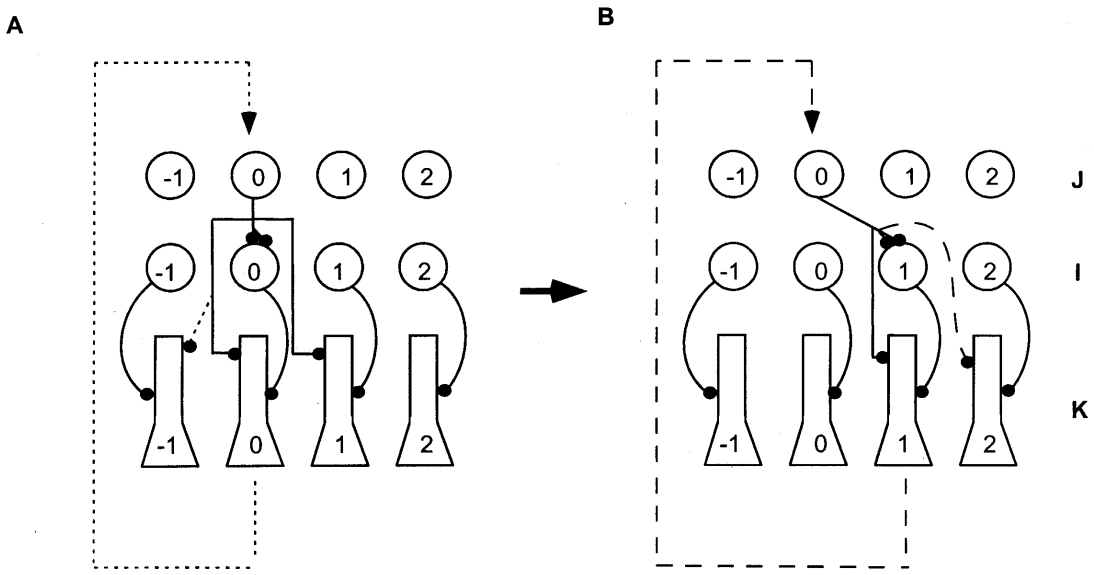

Fig 8. Generation of K cell circuitry by offline recalibration. Part A recapitulates the circuitry sketched in Fig 6A. If despite the operation of this circuitry an error does occur, with formation of a "mutant" synapse onto neurone I_1, and this new connection strengthens at the expense of the original connection (because the pattern of correlations that led to the original connection has changed), a different set of connections to and from layer K is required, if future errors in the strengthening of the new connection are to be prevented, as shown in Part B. In order to reconfigure the layer K connections from A to B, the connections shown dotted must be broken, and the connections shown dashed must be created. This can be done in a two stage process if the entire circuit is taken offline and suitable internally-generated recalibration signals are played into the J layer. First, individual J cells (for example J_0) should be strongly activated while the J-I connections are all rendered implastic, and the J-K connections are rendered plastic (these global plasticity changes could be procured through release of suitable neuromodulators such as acetylcholine or norepinephrine). This strong J_0 activation should in turn cause to fire all the I cells that are its current targets (in this case, I_1). This could be achieved if a wave of "burst": activity sweeps over the J layer. This will strengthen the J_0-I_1 connection, which will create (via uncontrolled error) the desired new J_0-K_2 connection. The unsupported J_0-I_{-1} connection withers. In the second stage, the plasticity of K-J connections is selectively enabled, and J cells are randomly activated (for example by random activation of cholinergic brainstem inputs). If the set of J cells that innervates I_1 (in the case shown, just J_0) happens to fire, then K_1 will also fire (since it detect the relevent correlations). If (due to previous uncontrolled errors) K_1 makes a connection onto J_0, this connection will be appropriately strengthened, while the unsupported K_0-J_0 connection will wither.

8. EVALUATION

The idea underlying these speculations is rather simple, though it has been little discussed. The creation of complex and precise neural networks requires that wiring errors be minimised, and that weight adjustments be anatomically specific. The size of any information-rich complex object, be it a genome,a neural network or a computer disk, is ultimately limited by the precisionwith which the information can be written. If new synapses created by strengthening existing connections do not inherit the original connectivity, they will impair network performance. It might be argued that if these new,

erroneous, synapses are “silent” they will not impair performance, while providing a reservoir of novel and potentially useful connections. However, since correlated activity across new silent synapses will cause unsilencing, network impairment cannot be avoided. In our terminology new connections are created as a result of errors in the strengthening of existing connections, but one could also regard them as coactivity-induced “sprouts”. If instead sprouting occurred at some activity-independent basal rate *S*, then a similar equation to Eq 5 would result, with the term ϕE replaced by *S*. Under these circumstances, the spread of synapses would depend on the difference, not the ratio, of the mesa and plateau fitnesses, each relative to *S*. Accurate connections could still be maintained by the circuitry of Fig 6, except that K_0 would have to compute the differences in the absolute levels of correlations, rather than the ratio.

One way to ensure anatomically specific learning is to build better synapses, with improved insulation, greater separation and larger numbers of key molecules. However some residual unspecificness is inevitable, and if neural correlations, deriving from subtle environmental regularities, are relatively weak, self organisation may fail entirely. Ultimately the useful size of any complex system is limited by the accuracy with which its components operate, and the neocortex, perhaps the most complex object known, is unlikely to be exempt. This suggests the possibility that the neocortex has developed some unusually effective way of minimising the consequences of inevitable synaptic learning errors. It seems unlikely that neocortical synapses embody a new error-free design principle, and more likely that instead some of the unusual features of thalamocortical circuitry are involved.

Our viewpoint is orthogonal to traditional discussions of neocortical function, which naturally focus on the issue of how circuits can explain perception, memory, decision and behaviour, and how such circuits can be established. We propose that much circuitry is instead devoted to noninformation processing tasks. In figs 6 and 7, “information processing” is being done by one set of connections (from layer J to layer I), while the other 3 sets of connections are being used to prevent adverse consequences of synaptic learning errors. None of this extra circuitry would be needed if there were no errors in synaptic learning. It would not be needed either if mistakes could somehow be “averaged out” over time; however, our analysis suggests that mistakes can only be averaged out if very strong correlations are present. The real world is sufficiently ambiguous, complex and noisy that efficient averaging is unlikely. Under favorable conditions (negligible error rates or strong correlation), our circuits default to a traditional “wide-open” learning condition.

Our viewpoint is also orthogonal to the notion that somehow random wiring leads magically to efficient information processing (Braitenbeg & Schuz 1991). Current evidence suggests instead that cortical wiring is very precise (Reid & Alonso 1995). In other situations there are indications that wiring may be less precise, especially during development (Chen et al 2001). For example, we have already alluded to the finding that while a typical lgn relay cell gets its major input from a single retinal ganglion cell, it receives minor input from one or two other ganglion cells as well. It is not clear whether such convergence is “deliberate” (so that lgn cells have non-relay functions) or

"accidental" (a result of imprecision in Hebbian wiring exacerbated by inevitable correlations in the firing of the "major" and "minor" inputs), though the finding that such overlap greatly decreases during development (Chen et al 2001) favours the latter view.

The circuitry and physiology that we have proposed are detailed and complicated, and although they are largely consistent with the sketchy information that is available, it will be important to subject both to experimental tests (Elliott, 2002). Is the logic itself faulty? We think there are two areas of potential weakness. First, we have not really justified the claim that learning errors can lead to complete failure of self-organisation. If one could guarantee that such errors never "run away", and at worse merely produce some controllable degradation of network performance, error avoidance would be less necessary. In particular, in the simple model presented in section 3, while errors render connections diffuse, the "correct" neurone always receives the most synapses, and progressive addition of alternative target neurones never completely prevents selective wiring. Second, in our diagrams neurones are conveniently lined up in rows, so that neighborhood relations are explicit. In reality neighborhood relations are less explicit, and presumably reflect the accidents of particular wiring histories. Nevertheless some neurones are still more likely error targets than others, and in this sense the neighborhood concept is valid. The real problem is that the neighborhood relations that are established for J-I connections must be echoed by J-K connections.

In summary, we propose that much thalamocortical circuitry exists to ensure accurate wiring in the face of anatomically imprecise learning rules combined with environmental complexity. Although our model is speculative and oversimplified it focusses on issues that have been neglected, and which might be relevent to the assembly of extremely complex neural networks.

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