

The resource consumption principle: Attention and memory in volumes of neural tissue

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ABSTRACT In the cerebral cortex, the small volume of the extracellular space in relation to the volume enclosed by synapses suggests an important functional role for this relationship. It is well known that there are atoms and molecules in the extracellular space that are absolutely necessary for synapses to function (e.g., calcium). I propose here the hypothesis that the rapid shift of these atoms and molecules from extracellular to intrasynaptic compartments represents the consumption of a shared, limited resource available to local volumes of neural tissue. Such consumption results in a dramatic competition among synapses for resources necessary for their function. In this paper, I explore a theory in which this resource consumption plays a critical role in the way local volumes of neural tissue operate. On short time scales, this principle of resource consumption permits a tissue volume to choose those synapses that function in a particular context and thereby helps to integrate the many neural signals that impinge on a tissue volume at any given moment. On longer time scales, the same principle aids in the stable storage and recall of information. The theory provides one framework for understanding how cerebral cortical tissue volumes integrate, attend to, store, and recall information. In this account, the capacity of neural tissue to attend to stimuli is intimately tied to the way tissue volumes are organized at fine spatial scales.

We have previously suggested that local volumes of neural tissue may act as cooperative processing units through the Ca^{2+} -dependent production and action of the membrane-permeant gas nitric oxide (NO) (1–4). In this paper, we extend this view of volume processing by considering the interactions that take place between different cellular compartments within a local volume of neural tissue.

Quantitative light and electron microscopy has established that the overwhelming fraction of any volume of cerebral cortical tissue is occupied by neural elements participating in synapses (>80%), (5) with less than half of the remaining volume as extracellular space (see ref. 6 for a more functional measure) (see Fig. 1). Located in this small extracellular space are atoms and molecules that, although necessary for the function of synapses, are distributed differentially between extrasynaptic and intrasynaptic compartments (e.g., calcium). In the specific case of calcium, the differential distribution is extreme with concentration ratios in the range of 10,000:1 pointing from extrasynaptic compartments to intrasynaptic compartments.

It is well known that transmission at central nervous system synapses requires calcium entry at presynaptic sites and is associated with calcium entry into postsynaptic elements (7). Estimates of calcium currents through pre- and postsynaptic channels strongly suggest that active synapses in a local volume of tissue will cause a transient but dramatic shift of calcium from the extracellular space into pre- and postsynaptic ele-

ments of active synapses (8). This conclusion is consistent with direct measurements of changes in extracellular calcium using ion-sensitive electrodes (9, 10, 11). These experiments have demonstrated millimolar-order changes in extracellular calcium subsequent to synaptic activity or glutamate application [e.g., from 2.0 mM to 1.4 mM (9) and from 1.25 mM to 0.08 mM (10)].

We see from the brief review above that the movement of calcium from the extracellular space into intracellular compartments (neural and nonneural) represents the removal or degradation of one resource known to be necessary for synapses to function (e.g., release of neurotransmitter upon the arrival of an action potential). Similarly, the movement of calcium back into the extracellular space would represent a replenishment of this resource.

BACKGROUND AND THEORY

Motivated by the physical possibilities outlined above, I propose here the hypothesis that, within a local volume of tissue, the resource is consumable by a subset of synaptic elements and is therefore in limited supply for the population of synapses residing in the volume. Over short time scales, this hypothesis suggests that the shift of resources into intrasynaptic and intradendritic compartments permits a local tissue volume to choose a set of functioning synapses at the expense of other possible sets of functioning connections. This proposal is called the “resource consumption principle,” and how the principle could relate in fundamental ways to long-term information storage and to attention is described below.

For the purposes of this paper, the focus is on the shift of calcium among various compartments; however, many factors could contribute to effective resource gradients. I ignore the detailed dynamics of this shift of calcium between extra- and intrasynaptic compartments so that some of its more important implications can be made clear (i.e., the examples below are not exhaustive with respect to the possibilities that exist in real tissue).

Resource Consumption Causes Competition in a Local Tissue Volume

The idea of volume-specific consumption of a shared, limited resource is illustrated in Figs. 1 and 2. Under the influence of signals impinging on a volume of tissue, those synapses that successfully shift calcium from the extracellular compartment into the intrasynaptic compartments will be more likely to transmit spontaneously or upon subsequent arrival of action potentials along parent axons (gray terminals in Fig. 1C). This resource shift has another important effect on the way local tissue volumes operate: action potentials invading terminals with little to no access to extracellular calcium are less likely to release transmitter (white terminals in Fig. 1C).

Within the local volume, those synapses that have consumed most of the available resource are at an advantage relative to connections nearby that have consumed little to none. Hence,

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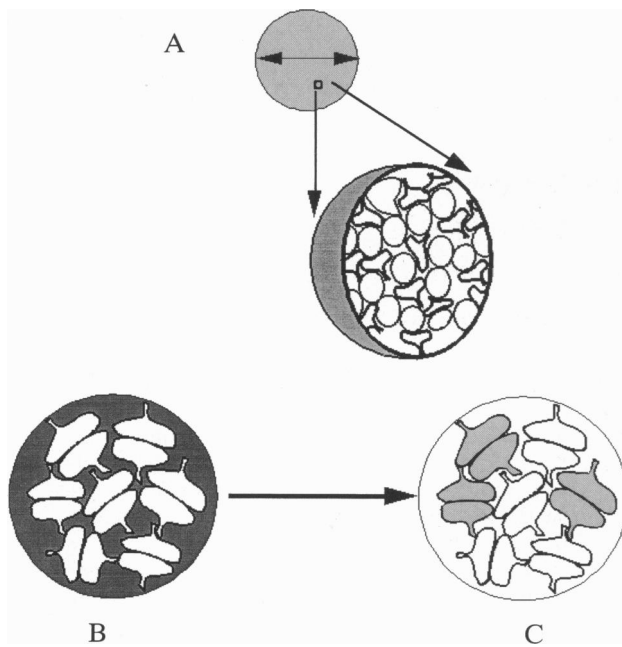


FIG. 1. Resource consumption principle: a minority of connections could consume a majority of limited resources available to a tissue volume. (A) The majority of any volume of cerebral cortex is made of neural elements participating in synapses. In the mammalian cortex, estimates of synaptic density range from 0.7×10^9 to 1.2×10^9 synapses per mm^3 . To give some notion of the scale and number of synapses, a volume of radius $36 \mu\text{m}$ (gray circle) contains $\approx 200,000$ synapses, and a subvolume of radius $3 \mu\text{m}$ (Inset) contains ≈ 100 synapses. In the expansion of the subvolume, synaptic elements are depicted at an approximately correct scale. The main point is that most notions of nearby in cortical tissue include a large number of synapses. As illustrated, the extracellular space is a minority of the total volume. (B) Expanded view of a part of the subvolume volume in A. Pre- and postsynaptic elements are shown in white, and the extracellular resource is represented by the gray background. There is a time scale over which atoms and molecules necessary for synaptic function, like calcium, could be in limited supply in the extracellular space under the influence of synaptic activity. Receptor and channel events on pre- and postsynaptic elements act at many time scales to remove calcium from the extracellular space. It is hypothesized that this movement represents a *consumption* of resources necessary for synapses to work. In this fashion, the subset of synapses capturing the resource tends to preclude consumption by other nearby synapses in the local volume. This consumption is possible because the volume of intrasynaptic compartments is significantly larger than the surrounding extracellular space. The result is that action potentials arriving at terminals after the resource has been consumed are simply ignored [i.e., do not cause the release of transmitter (white terminals)].

consumption by synapses of limited resources induces a powerful competition throughout a local volume. Over short time scales, the volume *attends* to the subset of connections that have consumed the majority of resource. Any factors that favor the capacity of one set of synapses to consume resource will tend to enable those synapses and tend to disable their local competitors. The competition would be augmented dendrites that sample the volume: activated dendrites that capture resource do so at the future expense of unactivated neighboring dendrites and synapses. Future changes in synaptic or cellular function that require dendritic calcium would be favored in those dendrites that consumed sufficient resource and would not be favored in those that captured little to none.

This way of viewing cerebral cortical tissue places neural signal processing squarely on the shoulders of tissue volumes: computations take place in parallel across numerous volume elements. These computations are in part defined implicitly by the three-dimensional arrangement of connections within each

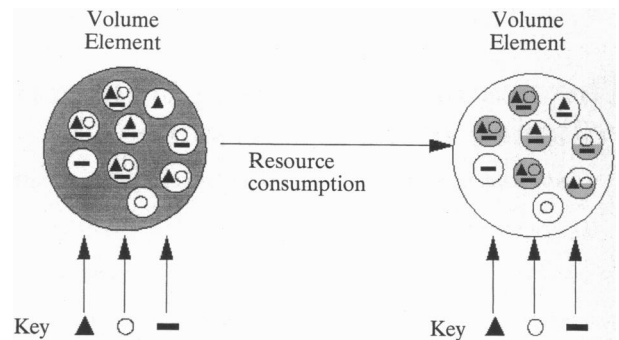


FIG. 2. Matching, integrating, and attending through resource consumption. (Left) Information converges on a volume element from three different sources (\blacktriangle , \circ , \blacksquare) each distributed throughout the volume. I propose that the diversity of receptor types, function, composition, link to intracellular cascades, time scales of action, etc., possessed by synapses represent a kind of combination lock that is matched (or not) by the state of the volume, which acts as the key. This match need not be exact. A match between the state of the volume (the key) and synapses in the volume is assayed by the degree to which a synapse consumes the limited resource available to the local volume (resource consumption principle in Fig. 1). (Right) Those synapses that best match the state of the volume will consume more extracellular resource and are put at a competitive advantage. Over short time scales, this competitive advantage would force the volume to “attend to” the current set of winning consumers. Over longer time scales, the successful synapses (triple matches) would be reproduced locally, thus permitting their combination locks to have greater representation in the volume. The unsuccessful competitors—i.e., those that matched but matched poorly (double matches)—would be removed. The synapses that did not compete at all (single matches and all others not shown) are ignored (see Fig. 3).

local volume element (1–4). This viewpoint places action potential production at the end of an enormous amount of analog processing and suggests that, even in the cerebral cortex, single spikes could carry far more information than previously suspected (but see ref. 12).

To summarize, we have appealed to three observations about volumes of neural tissue to generate a resource consumption principle by which local volumes of neural tissue operate: (i) the extracellular space represents a small fraction of any volume of neural tissue relative to intrasynaptic and intradendritic compartments that reside in the volume (Fig. 1), (ii) the extracellular space contains atoms and molecules in limited supply on short time scales that need to be shifted into synaptic elements in order for synapses to operate, and (iii) the shift in ii into a subset of synaptic elements can alter dramatically the availability of the resources to nearby synapses in the local volume.

The manner in which synapses are chosen as successful consumers of resources is specified below (Fig. 2) where we address two time scales over which resource consumption could have an influence: (i) neural signal integration at short time scales (≈ 10 – 1000 msec), and (ii) information storage at longer time scales (decision to store ≈ 1 – 100 min, with storage lasting indefinitely). In this paper, the two proposals are coupled strongly through the resource consumption principle; however, they could be viewed as separate theories.

Coupling Lock and Key Recognition to Resource Consumption

It is well known that synaptic boutons, dendritic spines, dendritic shafts, and cell bodies are covered with receptors of many sorts. Even in the absence of complicated considerations about the subtle functions of neurons and their local connectivity, the vast number and variety of interactions mediated through receptors seem to preclude any description about how

their collective state at one time could predict their collective state at a future time. If we focus precisely on the complexity of receptor distributions on synapses under the resource consumption principle described above, a possible role for such receptor diversity and the diversity of ensuing signals becomes clearer. For this simple example, we are omitting the complications of dendritic interactions, spike production, and dendritic structure.

Suppose that two neurons have at their disposal two different kinds of receptors (R_A and R_B) that they can express in both their dendrites and axonal terminals. Assume for the moment that, whenever receptor R_A and R_B binds its respective ligand (A or B), a unit quantity of limited extracellular resource (calcium in our example) shifts from the extracellular compartment into pre- and/or postsynaptic elements of the synapse. Let us now think of the collection of receptors on these terminals as a kind of *combination lock* and consider which terminals will gain the most resource given the *state of the volume*, which acts as the *key* to this lock. The *match* of the key and combination lock is "assayed" by the consumption of the limited resource available to the surrounding tissue volume. At some time scale, the synapses that match the key best will be able to function because they have consumed the necessary resource, whereas synapses that have not consumed resource will not function even upon the arrival of action potentials. This idea is made more concrete below and is illustrated in Fig. 2.

Suppose that each of the two cells above expresses receptors R_A and R_B in stable ratios characteristic for each cell: cell 1 expresses $10 R_A:2 R_B$, cell 2 expresses $2 R_A:10 R_B$. In Fig. 3, filled triangles denote terminals of cell 1 and open circles denote terminals of cell 2. Now consider the effect of putting two axonal terminals from each cell into three separate volumes of neural tissue.

As shown in Fig. 3, the terminals from each cell match best the state of different volumes (i.e., different keys). The matching process is assayed by the consumption of resource, which forces each volume to attend to a particular subset of terminals. Each tissue volume chooses a particular set of functioning connections in the context of the three signals illustrated in this example (A, B, C). Hence, by acting together, the matching and resource consumption provide a means to integrate the many signals that impinge on each volume or exist within terminals residing in the volume.

This example is a simplification of a more general notion of matching between keys and resident locks in a tissue volume. It should be noted that action potentials invading any particular synaptic terminal also act as part of the key for a local volume by inducing the consumption of calcium by that terminal. With this clearly in mind, long-range and short-range connectivity can be viewed as components of the combination lock of each synapse. We have excluded detailed consideration of this influence and instead emphasized the influence of receptor distributions to make a clear connection between the resource consumption principle and long-term information storage.

Longer Term Effects: Storing, Erasing, and Ignoring

An important issue now arises. Although resource consumption assays the match between lock and key on short time scales, longer-term effects require some long-term evidence of the interaction of a given volume state with its resident combination locks. In real neural tissue, one simple answer is to either reproduce the lock, remove the lock, or ignore the lock (Fig. 3).

The easiest way to reproduce a combination lock in a volume is to allow the axonal terminal to sprout (reproduce) locally and then continue to maintain the terminal. To remove a lock, a resource-deprived connection can simply be retracted (die). We require the removal of only those combination locks that competed for resource but competed poorly. Those synapses

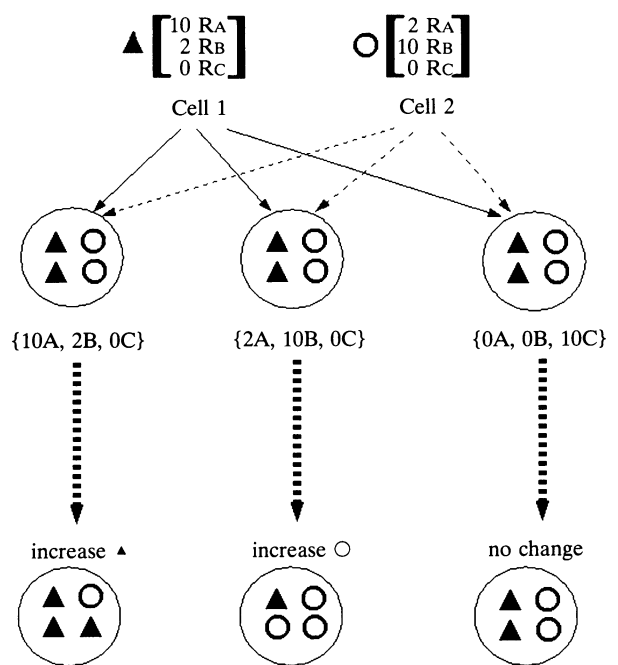


FIG. 3. The constructive nature of storage: reproducing, removing, and ignoring. Two cells (1 and 2) make synapses (\blacktriangle , \circ) in three separate volumes. Each cell expresses receptors R_A and R_B in stable ratios: $10 R_A:2 R_B$ (\blacktriangle) and $2 R_A:10 R_B$ (\circ). The key or state of each volume is shown in braces below each volume and includes the presence of another ligand C. In this example, we assume that each binding event moves one unit of resource into a synapse. In the volume on the left, each filled triangle will gain 12 units of resource and the open circles gain only 4; over time, this matching and consumption induces, through sprouting and retraction, an increase in the representation of the combination locks associated with the filled triangles. The converse is true in the center volume. In the volume at the right, neither synapse type recognizes the key presented to this volume. This example illustrates how a stable memory could be formed based on the relative representation of a synapse type (combination lock) in a given volume of tissue. This kind of memory would be stable to receptor and membrane turnover. Once a cell is committed to a sufficiently stable pattern of receptor expression, its terminals must simply be maintained for the memory to remain intact—the changes due to sprouting and retraction are purely local and are subsequently maintained as one ongoing function of a cell. Because of its dependence on stable receptor expression, this form of memory would exhibit a dependence on protein synthesis and normal gene expression.

that did not compete at all (i.e., did not consume any resource) are neither sprouted nor retracted; they are simply ignored. It is important to emphasize that the "sprout", "retract", or "ignore" decisions are purely local ones taking place at the targets and can therefore depend on many types of signals impinging on a target volume (Fig. 3).

From the point of view of the dendrites that sample the target volume, increasing the representation of a particular lock increases locally the synaptic weight—i.e., synapses from a given axon appear "stronger" in this volume in the presence of the correct key. Also, since there are more of these types of contacts, they are likely to induce a more rapid dendritic response, and, together they consume resource more rapidly. Through short-term resource consumption, the tissue volume is more likely to attend strongly to these connections in the presence of keys that they match. Synapses that matched a key but competed poorly appear "weaker" for the same reason: their representation in the volume is decreased. On short time scales, these terminals consume less resource upon subsequent presentation of the keys that they previously matched; therefore, tissue volume is less likely to attend strongly to these connections under a particular key.

There are other biologically plausible ways to maintain the synaptic strength changes in a local volume of tissue. We here suggest that the default condition is a minimal one: synapses of axons are maintained by the cell as one normal function of what the cell does. Given this fact, the long-term maintenance of a particular memory requires only that the cell continues to (i) maintain its terminals and (ii) ship receptors out in stable ratios. In this fashion, all or part of a synapse can be replaced without perturbing significantly its relative representation in a recipient volume of tissue—i.e., the storage is invariant to receptor and membrane turnover and actually takes advantage of detailed differences between complements of receptors on cells.

What Prevents the Takeover of One Lock Type in a Volume?

The resource consumption principle implicitly prevents one successful combination lock from taking over a given volume (Fig. 4). As proposed earlier, the extracellular resource is in limited supply on short time scales and is completely consumable by a subset of connections in the local volume. If a lock was replicated over and over again in a volume, then each copy of the lock gets less and less resource in the presence of a key that it matches. At some point, presentation of the key is matched by a large number of these duplicate locks in parallel and each lock consumes insufficient resource for further duplication (Fig. 4, panel 5). By assumption, the consumption of resource in insufficient quantities is exactly the condition that marks some fraction of these locks for retraction. In this manner, their number is normalized to an “appropriate range”

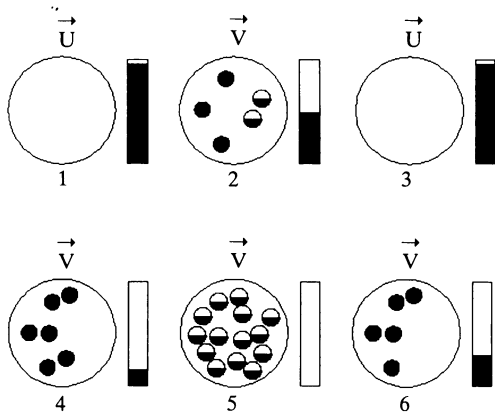


FIG. 4. The self-limiting nature of storage under the resource consumption principle. Local tissue volumes depicted beside a slider bar, which indicates the level of resource consumption for each key \vec{U} and \vec{V} . Panel 1, response of local volume to key \vec{U} which does not match any synapses in the volume. Panel 2, response of volume to \vec{V} , which has three good matches (●) and two poor matches (◐). Between 2 and 3, the good matches tend to sprout while the poor matches tend to retract. Panel 3, while sprouting and retraction take place, presentation of \vec{U} still causes no resource consumption. Panel 4, presenting \vec{V} now causes a stronger and possibly quicker response from dendrites sampling these synapses. Panel 5, \vec{V} continues to be presented causing the overrepresentation of combination locks that recognize volume state \vec{V} is self-limiting (normalized) since, at some point after multiple replications, these locks consume in parallel the vast majority of the resource upon presentation of the key \vec{V} . In this manner, no synapse consumes enough for further replication and some fraction of the synapses are marked for retraction. Panel 6, after retraction, presentation of \vec{V} causes the consumption of a level of resource within the working range of the volume. Many kinds of neural and nonneural elements could control the baseline level of the resource gradient and its speed of depletion and replenishment. Note that the event initiating sprouting or retraction is common: consumption of the extracellular resource.

for the volume (Fig. 4, panel 6). Defining precisely what is meant by an appropriate range and short time scales will require a more detailed analysis of the dynamics of these processes.

The Matching Process: Choosing Functioning Connections

We have described the matching process between the key and locks in terms that suggest a specific all-or-none assay of the degree of match. If the theory actually required such specificity in the matching step, then it would be untenable: it would be almost impossible for the system to construct the exact key needed to choose a particular set of functioning connections. The reason for this latter difficulty becomes clear when one considers the number of possible states of the synapses populating a tissue volume.

As stated earlier, there are many kinds of contributions to combination lock structure: local and long-range connectivity, along with receptor types, function, link to intracellular cascades, etc. Hence, the number of possible states per lock is expected to be high. Even if this number were modest, say 10, the high density of synapses in the mammalian cerebral cortex ensures a large number of possible states per volume of tissue. For example, if there are 10 states per lock, then a tissue volume of radius 12 μm (>7000 synapses) can be in 1 out of more than 10^{7000} states. Although this number ignores various kinds of degeneracies, it is sufficiently large to suggest that the number of possible states in small tissue volumes is very high.

There must exist, therefore, a mechanism that adaptively controls the stringency of the matching process—i.e., changes the degree of match required for a synapse to consume a quantity of resource sufficient to operate. One way to view this matching process is to let the match between the key and lock determine the *affinity* of the lock for resource (Eq. 1 below). The affinity of a lock for resource thus expresses the propensity of the synapse to acquire resource when resource is available in the surrounding volume of tissue. It is important to note that a lock may match well the key for its volume, but the resource may have already been consumed earlier. In this fashion, one set of synapses would be ready to operate rapidly once the resource was sufficiently replenished.

A key can be represented as a vector $\vec{V} = (v_1, v_2, \dots)$. The term key is used instead of “input vector” because each component is envisioned as acting like a separate fluid available homogeneously throughout the volume. Subsets of the components may possess stationary statistics and others may not. Let $\vec{S}_j = (s_1, s_2, \dots)$ denote the combination lock of synapse j . Under the constraints imposed by the key \vec{V} , the affinity of lock j can be expressed as

$$A_j(\vec{V}) = f(M(\vec{V}, \vec{S}_j), T), \quad [1]$$

where $A_j(\vec{V})$ denotes the affinity of lock j for resource and f is a function of the match M and is a nondecreasing function of another parameter T . $M(\vec{V}, \vec{S}_j)$ measures the match between the key \vec{V} and the lock \vec{S}_j . T is envisioned as a kind of temperature parameter that controls the stringency of the match. f and M obtain a dependence on time through \vec{V} and the kinetics of the matching, consumption, and replenishment processes.

At high T (fixed M), many candidate synapses are recruited as potential consumers of resource (low stringency). As T is decreased, the stringency for the resource consumption increases—i.e., to achieve the same affinity, the match must be higher at lower values of T . The rate at which T increased and decreased could then come to control many aspects of local processing. For example, a local volume that maintained T high could give relatively promiscuous responses to many keys that it experienced, whereas other volumes that perform more precise processing may do so by keeping the average T relatively low.

One biological candidate for stringency control is the membrane-permeant gas nitric oxide (NO) that is produced by a calcium-dependent enzyme and moves isotropically and rapidly throughout a local volume of tissue. NO is known to synergize with calcium to enhance neurotransmitter release. Stringency control could therefore be both local and global because NO is made locally in the cortex and can be delivered by diffuse ascending systems that originate in neurons in the midbrain and basal forebrain. Hence, NO production in a volume would recruit initially all possible matches for a particular key, thereby acting to reduce the stringency of the matching process. As the NO levels declined due to destruction and diffusion, the stringency for the match would increase, and only those synapses that matched well would continue to capture resource. This process would allow a rapid (logarithmic in time) divide and conquer strategy for finding a set of synapses that fit well a key presented to the volume.

Such a signal for stringency control implicitly encourages neighboring volumes to seek functioning synapses at similar stringency levels because $T \equiv T(\vec{r}, t)$ evolves according to a diffusion equation

$$\frac{\partial T(\vec{r}, t)}{\partial t} = -D\nabla^2 T(\vec{r}, t) - \kappa T(\vec{r}, t) + G(\vec{r}, t). \quad [2]$$

The first term on the right represents the passive diffusion of T , the second represents the spatially uniform exponential decay of T , and the third term represents the increase in T due to exogenous sources. ∇^2 is the Laplacian operator, D is the diffusion constant, \vec{r} indexes the location of the volume experiencing \vec{V} , t is time, κ controls the rate of exponential decay of substance, and $G \equiv G(\vec{r}, t)$ is the global (exogenous) delivery rate of substance.

DISCUSSION

We have suggested how the fine scale organization and operation of volumes of neural tissue could provide powerful building blocks for neural signal integration and stable long-term storage of information. Through the proposed resource consumption principle, the basic capacity of local tissue volumes to attend to a subset of connections provides a new way to view higher level attentional effects. The theory therefore suggests a reexamination of the possible neural substrates for attention: a concept that until recent years was exclusively part of the vocabulary of psychology. Low level attentional effects now become a fundamental feature of local volumes of tissue. These possibilities await future theoretical and experimental work.

The resource consumption principle, when coupled to the matching process, collapses signal integration, attention, and storage into a single general mechanism for processing by a local volume of cortex. It seems apparent that the general mechanism also has important implications for cortical development and for the general principles by which the cortex organizes and reorganizes. For example, in the mammalian visual cortex, there is a poorly understood influence of catecholamine and acetylcholine delivery on activity-dependent

development (13–16). It is known that at least one of these inputs is necessary for normal visual cortical plasticity (15). Under the current theory, the matches that take place in volumes of visual cortex would depend in part on combination locks composed of various acetylcholine, catecholamine, and glutamate receptors. The matches would also depend on direct visual input from the thalamus. As assayed by resource consumption, the matches that work cause an increase in the representation of matching synapses. In this particular example, the subsequent function of the structures that developed would depend on glutamatergic, cholinergic, and catecholaminergic inputs all potentially carrying different kinds of information. If, for example, fluctuating acetylcholine delivery carried the signal “your eye is about to move”, then the circuitry that develops would accrue a dependency on such information.

The theory raises many interesting possibilities for the roles that glial cells and other nonneural components can play in neural processing, memory, attention, etc. Through their capacity to set, replenish, and/or buffer local calcium levels in a local volume, they can exert a powerful influence on the kind of processing accomplished by a given piece of tissue. In this sense, all the elements in a volume of tissue contribute, as a system, to integration, attention, and memory.

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1. Gally, J. A., Montague, P. R., Reeke, G. N. & Edelman, G. M. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 3547–3551.
2. Montague, P. R., Gally, J. A. & Edelman, G. M. (1991) *Cerebr. Cortex* **1**, 199–220.
3. Montague, P. R. & Sejnowski, T. J. (1994) *Learn. Mem.* **1**, 1–33.
4. Montague, P. R., Gancayco, C. D., Winn, M., Marchase, R. B. & Friedlander, M. J. (1994) *Science* **263**, 973–977.
5. Schuz, A. & Palm, G. (1989) *J. Comp. Neurol.* **286**, 442–455.
6. McBain, C. J., Traynelis, S. F. & Dingledine, R. (1990) *Science* **249**, 674–677.
7. Hille, B. (1992) *Ionic Channels in Excitable Membranes* (Sinauer, Sunderland, MA).
8. Vernino, S., Amador, M., Luetje, C. W., Patrick, J. & Dani, J. A. (1992) *Neuron* **8**, 127–134.
9. Benninger, C., Kadis, J. & Prince, D. A. (1980) *Brain Res.* **7**, 187, 165–182.
10. Pumain, R. & Heinemann, U. (1985) *J. Neurophysiol.* **53**, 1–16.
11. Heinemann, U. & Stabel, J. & Rausche, G. (1990) *Prog. Brain Res.* **83**, 197–214.
12. Bialek, W., Rieke, F., de Ruyter van Steveninck, R. R. & Warland, D. (1991) *Science* **252**, 1854–1857.
13. Kasamatsu, T. & Pettigrew, J. D. (1976) *Science* **194**, 206–209.
14. Pettigrew, J. D. & Kasamatsu, T. (1978) *Nature (London)* **271**, 761–763.
15. Bear, M. F. & Singer, W. (1986) *Nature (London)* **320**, 172–176.
16. Gu, Q. & Singer, W. (1995) *Eur. J. Neurosci.* **5**, 475–485.