Abstract

We investigate a possible functional role of glial cells as information routing devices of the cerebral cortex. On the one hand, functionally motivated models of neural information processing were lately suggested which rely on short-term changes of connections between neural modules to dynamically route neural activity. Although successful in practice, the routing mechanisms of these models require synaptic efficacy control of large sets of synapses that is difficult to implement neurally. On the other hand, recent experiments show an active role of glial cells (astrocytes) in the interaction with large numbers of synapses. Astrocytes are sensitive to neurotransmitters released by the presynaptic terminal and in turn can influence synaptic efficacy by release of so called gliotransmitters. An analysis of the most recent literature shows that glial cells are a well-suited and natural candidate for the implementation of information routing mechanisms.

Keywords: Astrocytes; Information routing; Visual object recognition; Calcium signaling; Tripartite synapse; Synaptic modulation

1. Introduction

Glial cells are enjoying increasing attention from the neuroscience community since recent experiments suggested an active role of glial cells in neural information processing. The predominant glial cell type in the central nervous system (CNS) are astrocytes which constitute approximately 50% of the mammalian brain’s cells. Astrocytes are located in close relationship to neurons and envelope synapses with their processes thereby forming a complex anatomical network. Traditionally astrocytes have been viewed as passive elements, providing mechanical and metabolic support for neurons, as they are unable to fire action potentials. But astrocytes display another form of excitability based on intracellular calcium (Ca$^{2+}$) elevations. These so called calcium waves can be triggered and modulated by neurotransmitters released by neurons (for review see Perea & Araque, 2005) and quickly propagate within the cell or even to neighboring astrocytes. In turn, a propagated calcium signal stimulates the astrocyte to release chemical transmitters itself. These are called gliotransmitters and include various molecules, e.g., the major excitatory neurotransmitter glutamate (for review see Araque & Perea, 2004). Furthermore, there is increasing evidence that gliotransmitters released at a synapse may be able to modulate synaptic transmission of neural activity (for reviews see Araque & Perea, 2004; Auld & Robitaille, 2003; Newman, 2003).
Taken together, recent findings in glial cell research clearly suggest that astrocytes are able to react to neural activity and to transmit this information to other synapses, thereby providing a so far unknown anatomical pathway for information processing. This formerly unknown active part of glial cells stands in contrast to the traditional view that glial cells are merely maintaining the right environment for neurons but do not directly take part in information processing of the CNS. Neural modelers, therefore, nearly exclusively have relied on computations related to well-known properties of neurons, which restricted neural network models on the short time scale to static connectivity.

An exception, in this respect, are neural network models which suggest dynamic connectivity changes between different levels of neural processing. As models for visual processing these systems (see, e.g., Lücke, 2005; Olshausen, Anderson, & Essen, 1993; Wiskott & von der Malsburg, 1996; Zhu & von der Malsburg, 2004) possess active mechanisms to control synaptic connections in order to route sensory information to appropriate downstream units for further processing. Thereby, these correspondence-based systems actively address the problem of invariant visual object recognition, and various technical applications (Lades et al., 1993; Messer et al., 2004; Wiskott, Fellous, Krüger, & von der Malsburg, 1997) represent state-of-the-art object recognition technology. Although successful in practice, the neural implementation of routing mechanisms, i.e., the control of efficacy of large sets of synapses, has become a major challenge.

In this paper we will discuss a possible role for astrocytes in controlling synaptic efficacy and show why the functional properties of glial cells might provide a new and natural solution for the implementation of neural information routing.

2. Models of information routing and neural implementations

Attention is the mental action of focusing on relevant inputs while filtering out information that is currently irrelevant. In visual attention, at any time, only a small fraction of the information received at the retina is important to higher-level cortical areas for processing. Because the relevant visual information could appear anywhere on the retina, at any size and orientation, an attentional mechanism must be able to deal with these variations. This invariance problem is also the challenge in artificial visual object recognition. Shift invariance, for example, allows the recognition of a person independent of the exact location of the perceived image on our retina. Neural network models, such as associative memory models (Hopfield & Tank, 1986), usually have great difficulties to address this problem because of their limited generalization abilities. Many artificial object recognition systems achieve invariance by feed-forward computation of features that are insensitive to changes, e.g., of object location, using static connectivity between layers of processing (e.g., Elliffe, Rolls, & Stringer, 2002; Fukushima, Miyake, & Ito, 1983; Mel, 1997; Westphal & Würtz, 2004). Although these feature-based methods may be able to recognize simple objects, an increasing effort is made to incorporate attentional mechanisms into the systems to allow the application to more complex input (see Itti, Rees, & Tsotsos, 2005, for an overview). The more direct correspondence-based method is based on the dynamic routing of the object information to a standard position in higher-level cortical areas (e.g., Anderson, Essen, & Olshausen, 2005; Lücke, 2005; Olshausen et al., 1993; Zhu & von der Malsburg, 2004). By definition these methods integrate sensory and model information. In sharp contrast with feature-based methods, the correspondence-based methods preserve the relative spatial relationship between elements of the object, information which is very valuable for object decomposition or motor control in subsequent processing steps (Goodale & Humphrey, 1998; Zhu, 2004).

The simplified network model of Fig. 1 illustrates information routing between two areas, an input layer (primary visual cortex) and an assimilation layer for the integration of sensor and model-based information. The visual image is received by the retina R that transmits light intensities via the afferent visual system to an array of feature detectors I1–I6 in the primary visual cortex. Each feature detector consists of a collection of neurons whose activity distribution encodes a texture on the corresponding part of the retina. In primary visual cortex such a collection of cells is conceptually often referred to as hypercolumn (Hubel & Wiesel, 1977) or macrocolumn (Lücke & von der Malsburg, 2004; Mountcastle, 1997). The image information is transferred via the feature detectors’ synapses to the next higher layer of processing made up of neuron populations A1–A4.

Let us for simplicity consider shift invariant recognition for one-dimensional input. Let abstract models of one-dimensional objects be neurally stored as combinations of four features. In the case of Fig. 1 images of N different persons are stored as object knowledge. As input the system gets a combination of six features. Because of the restriction to shift invariance the image of the person is either received by units I1–I4, I2–I5, or I3–I6. Each abstract feature unit A_i is therefore connected to the three input units I_i, I_{i+1}, and I_{i+2} where its corresponding feature can potentially appear. When an object appears at one of the three potential positions, the corresponding synapse should be enhanced while the other synapses should be suppressed.

For static interconnectivity these multiple connections would cause the problem of signal interference. For example, unit A1 in Fig. 1 is perturbed by background features represented by units I1 and I2 whereas, e.g., unit A4 is perturbed by other features of the person’s image. To attend to the relevant input and suppress perturbations, correspondence-based systems apply mechanisms to enhance groups of synapses that actually convey relevant object information and to down-regulate others. These mecha-
nisms are driven by object knowledge and the stimulus itself.

Shifter circuits (Anderson & van Essen, 1987; Olshausen et al., 1993) use control units (control neurons in their terminology) that regulate synaptic efficacy of groups of synapses more or less globally. In the example of Fig. 1, a population of control units (dotted circle) would activate one of the three groups of synapses $\alpha$, $\beta$, or $\gamma$ by multiplicative interaction between synapses of the control units and the synapses of input units. Although in Olshausen et al. (1993), it is speculated how such interactions might be implemented, no satisfying answer could be given.

Dynamic link matching (DLM) systems use local control of synaptic efficacy (dotted horizontal arrows in Fig. 1). Depending on similarities between input and abstract model features across the groups $\alpha$, $\beta$, and $\gamma$, the corresponding group of synapses is selected and the system attends to the actual position of the object on the retina $R$. The local similarity computation and inner-group interaction is implemented using mechanisms such as a separate lateral Mexican hat interaction (Wiskott & van der Malsburg, 1996), local groups of links called maplets (Zhu & von der Malsburg, 2004), or by using a local control unit for each abstract feature unit $A_i$ (Lücke, 2005). In all DLM systems more or less direct communication between synapses is required whose neural implementation remains unclear.

To illustrate the fundamental difficulties for the neural implementation of synaptic transmission control, consider the general situation that a group of target neurons receives input from a group of presynaptic input neurons (Fig. 2). For information routing we need a mechanism that allows to manipulate the synaptic efficacies of groups of synapses. At first thought, inhibitory interneurons seem to be a good candidate for such a control. E.g., in cortex some types of inhibitory neurons target preferably the axon hillock of neurons (see, e.g., Silberberg, Grillner, LeBeau, Maex, & Markram, 2005, for review) and are thus in a position to regulate or rather deactivate these neurons’ synapses. This type of presynaptic regulation would affect all of the potentially thousands of synapses of an input neuron. However, as discussed in the context of simple translation invariance in vision (Fig. 1), the groups of synapses that have to be controlled for the required computations connect pairs of different pre- and postsynaptic neurons (gray diagonal ellipse in Fig. 2). I.e., the synapses of one presynaptic neuron are heterogeneously influenced. The control by axon hillock inhibition, by contrast, would homogeneously change synaptic efficacy of all synapses of the presynaptic neuron (control $C_1$ in Fig. 2). Another type of control can be implemented by inhibition on the postsynaptic side. In cortex some types of neurons preferably target the dendritic tree of their target neurons near the soma (see, e.g., Douglas & Martin, 2004; Silberberg et al., 2005, for recent reviews) and are thus in a position to postsynaptically regulate efficacy of incoming activity. This would affect a group of potentially thousands of synapses of the same dendritic tree (control $C_2$ in Fig. 2). But again the desired control is not implementable in this way because the postsynaptic inhibition near the soma homogeneously affects all synapses connecting to the dendrite and does not selectively affect specific subsets of these synapses as required.

A somewhat more advanced control would be a synaptic modulation at intermediate distances from the soma of the postsynaptic neurons. If we assume linear (non-branching) dendrites, even this control does not provide the mechanism to heterogeneously control specific groups of synapses. The control at one point of a linear dendrite will
always affect all synapses further away from the soma (see control $C_3$ in Fig. 2). Consequently we are only able to neurally implement the required control if we use controlling synapses at specific positions of specific branches in the dendritic trees of the target neurons. Moreover, the synapses of the input neurons have to be appropriately sorted to the different branches. In addition to this spatial arrangement the controlling synapses have to be of a fundamentally different type. Rather than linearly contributing to the input of the postsynaptic neuron as is usually assumed for synapses from input neurons, control synapses have to act in a non-linear, presumably multiplicative, fashion. Finally, the timing of postsynaptic potentials of control synapses has to be precise. Especially for the non-linear control of groups of synapses, coordinated arrival times of action potentials at control synapses are required. This problem becomes more severe for long feed-back loops to control units as required in, e.g., shifter circuits.

In summary we are confronted with the following situation: on the one hand, the control of groups of synapses across dendrites allows to implement attentional mechanisms which have proven to be a successful strategy for invariant object recognition. More generally, the computational capabilities of a neural network with dynamic modulation of synapses across different dendrites by far exceeds the computational power of networks with static connectivity. On the other hand, the implementation of intra- and inter-dendritic control of groups of synapses seems to require a specific machinery of special spatial and temporal arrangements of input and control synapses. The control synapses are required to modulate the activity induced by afferent synapses in a non-linear multiplicative way. Extending the neural network by introducing additional interneurons is an option that would merely transfer the burden of directing different synapses to specific dendritic branches to that of directing different synapses to specific neurons. The same applies to the relative positioning of control synapses. Furthermore, more complex synaptic efficacy control for more complex routing, e.g., as required by rotation and scale invariance in vision, would entail even more complex and specific networks with increasing numbers of interneurons that would be increasingly difficult to justify. At this point, recent physiological findings in glial cell research offer an interesting alternative for the implementation of synaptic efficacy control. Increasing evidance was found that astrocytes actively participate in synaptic transmission by forming what is called tripartite synapses, i.e., in addition to the pre- and postsynaptic neuron they represent a third active and presumably non-linear component of synaptic transmission. Moreover, astrocytes are anatomically in an ideal position for the required control of synaptic efficacy by connecting thousands of synapses of different neurons on different dendrites.

3. Glial cells for synaptic efficacy control

Astrocytes are the most numerous group of glial cells in the brain and are located in close anatomical relationship to neurons. Originally glial cells were considered to only
function as mechanical support for neurons, as expressed by the name ‘glia’, the Greek word for glue. Later it was found that glial cells play important roles in providing the right biochemical environment for neurons, for example by exchanging metabolites or buffering extracellular potassium. However, it is well known that astrocytes are not able to fire action potentials and this is probably why they have been categorized as exclusively concerned with ‘secondary’ tasks instead of actively participating in cognitive functions. But during the past years new interest in the functional properties of glial cells has been evoked by findings of intracellular calcium signals in astrocytes. These can be locally restricted to one region of the cell or propagate as so called calcium waves to other regions or even to neighboring astrocytes (Cornell-Bell, Finkbeiner, Cooper, & Smith, 1990). Various studies have demonstrated that calcium signals can be evoked by neurotransmitters released by neurons and in turn result in the release of gliotransmitters by the astrocyte thereby providing a previously unknown mechanism of information transfer. Furthermore there are strong indices that gliotransmitters released at a synapse are able to influence neural information processing by modulating synaptic transmission. More generally speaking, this means that astrocytes react to synaptic activity and transmit the information via calcium signaling to other groups of synapses where they regulate synaptic efficacy. Anatomically the complex network of astrocytes and neurons puts them in an ideal position for mutual information exchange: each astrocyte is composed of a cell body and of several long and widely ramified processes which closely surround neurons and envelope synapses. The discovery of this close anatomical relationship and recent findings of functional properties of astrocytes have lead to the new concept of the ‘tripartite synapse’ (Araque, Parpura, Sanzgiri, & Haydon, 1999) which consists of three functional elements: the pre- and postsynaptic neuron and the surrounding astrocyte. Each astrocyte can cover synapses of several neurons and each neuron may have its synapses covered by different astrocytes. One single astrocyte can cover a total of about 140,000 synapses (Buschong, Martone, Jones, & Ellisman, 2002). The complexity of this anatomical network of neurons and astrocytes makes it seem plausible that it provides important functions in the information processing of the CNS.

Moreover, neurophysiological imaging studies have indicated that calcium waves within astrocytic processes are restricted to subcellular pathways called microdomains that can function relatively autonomously (Pasti, Volterra, Pozzan, & Carmignoto, 1997). In addition, the existence of morphological subcellular compartments could be demonstrated by electron microscopy in astrocytes of the cerebellum (Grosche et al., 1999). These compartments have a very complex, highly branched surface and wrap around synapses. Investigations of Ca2+ signaling in response to synaptic activity showed that the Ca2+ signals indeed followed a spatial pathway corresponding to the anatomical microdomains as seen by microscopy. Therefore it seems likely that synapses might be specifically connected via independent microdomains which allows their directed interaction, mediated by a calcium signal.

Consider the illustration in Fig. 3 where the gray ellipses symbolize three groups of synapses covered by three microdomains within an astrocyte’s process. Each functionally related subset of synapses is specifically connected by the same microdomain.

In the following we will describe in more detail how neural activity at a synapse can induce a calcium wave in the surrounding astrocyte and how this signal can be transmitted to other synapses covered by the same astrocytic microdomain. As said before, astrocytes express receptors for various neurotransmitters released by neurons including glutamate, GABA, norepinephrine and acetylcholine (Araque & Perea, 2004; Auld & Robitaille, 2003; Newman, 2003) and it has been shown that calcium waves in astrocytes can be triggered by neurotransmitters both in cell culture and intact tissues (for review see Perea & Araque, 2003). When an action potential arrives at a synapse which is enveloped by the astrocyte’s process, an excitatory neurotransmitter gets released. The neurotransmitter activates receptors on the astrocytic cell membrane. Activation of a receptor can lead to an increase of intracellular Ca2+ in two possible ways, both of which have been described in astrocytes: the first receptor class, called ionotropic receptors, directly raises the cell membrane’s conductance for calcium ions which results in an inward current of Ca2+ from the extracellular space into the cell. Another receptor class called metabotropic receptors stimulates the intracellular formation of inositol triphosphate (IP3). IP3 is a messenger molecule which induces the release of Ca2+ ions from intracellular stores. In turn, the elevated Ca2+ will activate the enzyme phospholipase C which results in further formation of IP3. This self-enhancing mechanism is also very important for the propagation of the calcium signal. It can be assumed that a certain threshold of Ca2+ levels exists which is necessary to activate this mechanism and finally leads to a self-amplifying Ca2+ release into the cytoplasm (Venance, 2005).
Stella, Glowinski, & Giaume, 1997). Probably, activation of few single synapses will not be sufficient to generate a calcium signal. But the release of excitatory neurotransmitters by many of the synapses covered by the astrocytic microdomain could, by summing the single effects, lead to a Ca\(^{2+}\) elevation which exceeds the threshold, thereby generating a calcium wave which will rapidly spread through the microdomain. Thus the incoming excitatory postsynaptic potentials (EPSPs) at the synapses are combined to a glial calcium signal.

How can the glial cell in turn modulate synaptic transmission of the synapses it covers? As said above, astrocytes can release a number of different gliotransmitters including D-serine, Adenosine Triphosphate (ATP), Prostaglandin E2 and the excitatory neurotransmitter glutamate (for review see Araque & Perea, 2004). Various effects of gliotransmitters released from astrocytes at the synapse have been described. For example, gliotransmitters may modulate synaptic transmission by influencing the excitability of the postsynaptic neuron or by regulating the neurotransmitter release from the presynaptic terminal (for reviews see Araque & Perea, 2004; Auld & Robitaille, 2003; Newman, 2003).

The best examined mechanism in this context is the modulation of synaptic activity by glutamate, which we will describe as an example: It has been shown that the release of glutamate by astrocytes works via a Ca\(^{2+}\) dependent pathway (Pasti, Zonta, Pozzan, Vicini, & Carmignoto, 2001) and indeed, it could be demonstrated in electrophysiological studies that the elevation of intracellular Ca\(^{2+}\) levels as caused by a calcium wave leads to a release of glutamate by the astrocyte. One important example for a possible modulation of synaptic activity by glutamate is the induction of postsynaptic slow inward currents (SIC) which can be evoked in adjacent neurons by an astrocytic calcium elevation. These directly cause a depolarization of the postsynaptic membrane, which can contribute to trigger action potentials in the postsynaptic neuron (Araque, Parpura, Sanzgiri, & Haydon, 1998a; Hassinger et al., 1995). Additionally, glutamate released by astrocytes has been shown to increase the frequency of so called miniature postsynaptic currents (mPSCs) (Araque, Sanzgiri, Parpura, & Haydon, 1998b). It is known that alterations in the frequency of mPSCs are usually associated with changes in the probability of presynaptic transmitter release. Therefore, it can be assumed that glutamate released in response to astrocytic calcium elevations may increase the probability of transmitter release from the presynaptic terminal.

Various other groups have demonstrated glial modulation of synaptic activity mediated by other gliotransmitters or in different nervous tissues (for reviews see Araque & Perea, 2004; Auld & Robitaille, 2003; Newman, 2003). Taken together these results strongly suggest that astrocytes are capable of modulating neural transmission.

For the abstract situation in Fig. 3 this implies that the activity in a group of incoming synapses can, via the stimulation of their common microdomain, enhance their efficacy whereas synapses of microdomains that receive few action potentials can remain relatively inefficient. More specifically, regarding the example of Fig. 1, the simplest scenario would be an astrocytic process with three microdomains α, β, and γ that covers the three groups of synapses. Depending on the activity of the synapses, specific microdomains can be sufficiently stimulated and enhance the efficacy of all synapses in their areas of influence via calcium signaling whereas influences of other groups of synapses remain relatively weak. In Fig. 1, the presentation of the stimulus leads to a high activity of input units I\(_3\) to I\(_6\) which in turn results in microdomain γ receiving the highest input. By calcium-induced gliotransmitter release, microdomain γ can therefore strengthen synaptic efficacy and is thereby able to down-regulate the relative influence of the input from the irrelevant groups α and β. The system is thus attending to the relevant information.

This mechanism can be improved by simultaneously using recurrent connections from the model domain. If the activity of synapses in a microdomain does not depend on the activity of synapses from the input layer alone but also from model layer synapses, initial activity differences between groups of synapses can be amplified via an autocatalytic feedback loop. At the same time, combination of sensory and model input can suppress undesired influences of structured background.

In summary, astrocytes and their microdomains provide mechanisms that define and enable the control of groups of synapses. As the network of astrocytes and microdomains exists in addition to the network of axons and dendrites, it is directly possible to control groups of neural connections of different pairs of input and target neurons. No specific neural architecture with synapses sorted to the right locations on dendrites or sorted to the right interneurons is required. Furthermore, no specific assumptions about spike timing and non-linear control of synapses are necessary. The activity in a group of synapses covered by a microdomain can directly enhance synaptic efficacy in this and associated neighboring groups. These direct synapto-synaptic interactions are well-suited to implement the routing of information described in various realizations of DL.M, shifter circuits, and other correspondence-based systems. Non-linearity of astrocytic control arises from the nature of tripartite synapses where the astrocytic part can naturally act as modulator without affecting other synapses on the same dendrite. Specific spike timing is not required because of the different calcium based form of excitability in astrocytes.

4. Discussion

Starting by analyzing dynamic synaptic control as the crucial property in correspondence-based object recognition systems we discussed a possible functional role of astrocytes as information routing devices for neural processing. It has been argued that information routing is
not required for object recognition and that networks with information routing are not appropriately modeling neural processing. However, even research projects that have once started with purely feed-forward models of visual processing are increasingly attracted to concepts of attention (see Itti et al., 2005, for a review) and thus, more or less directly, to information routing.

For short-term synaptic routing, other mechanisms, based, e.g., on different types of inhibitory neurons, were discussed. Inhibitory neurons which target the axon hillock of neurons or target the dendritic trees of neurons near the soma are in a position to regulate the synaptic efficacy of large sets of synapses. These mechanisms were, however, found to be too limited to implement the required more sophisticated and heterogeneous control of synapses. Compared to these mechanisms, architectures with regulation within and across dendrites are far more capable computational structures (see Mel, 1992 & Olshausen et al., 1993, for discussions). However, as discussed above, this means that synapses acting non-linearly, e.g., multiplicatively, have to be connected at the right positions of the dendritic tree and act at the right time to implement gating mechanisms as required from networks such as Anderson and van Essen (1987); Olshausen et al. (1993); Wiskott and von der Malsburg (1996); Zhu and von der Malsburg (2004); Lücke (2005) (see Elliffe et al., 2002, for a critical discussion).

Glia cells, in contrast, are directly interacting with action potential transmission by calcium-mediated modulation of synaptic efficacy, a process which is different from the presumed linear summation of excitatory postsynaptic potentials of different synapses. No artificial subdivision of synapses into linear and non-linear groups is required. Implementations of synaptic regulation on the basis of glial cells does, furthermore, not require precise location and timing of control synapses to account for the right non-linear influence at the right time and at the right location relative to the position and activity of stimulus-driven synapses. Interneurons can still play an important role for information routing, however. They can actively participate in the integration of sensory and model information, and in realistic networks they can support communication between larger or distant groups of controlled synapses. In this way interneurons can account for a fast regulatory control that is otherwise limited by the relatively slow propagation of calcium signals through networks of astrocytes (see Verkhratsky, Orkand, & Kettenmann, 1998, for review). Interneurons are thereby helping astrocytes and their microdomains to coherently control and route neurally conveyed information for further processing. Information processing in the brain might thus consist of two important integral parts: (1) neural information transmission and integration and (2) glial control of information flow.

An increasing number of lately suggested neural network models use indirect attentional mechanisms (see Itti et al., 2005 for review) or active information routing (see Anderson et al., 2005; Lücke, 2005; Olshausen et al., 1993; Zhu & von der Malsburg, 2004) and are by many believed to represent the so far most realistic models of neural processing. But it has taken a long time for neural modelers to build networks that actively manipulate synaptic efficacy on a short time scale and the mechanisms are still debated – maybe because crucial devices to explain the functionally required mechanisms have not been found or recognized.

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References


Anderson et al., 2005; Lücke, 2005; Olshausen et al., 1993; Zhu & von der Malsburg, 2004) and are by many


