Primer: Neuronal energy use and brain evolution

Tania Quintela-López*, Hiroko Shiina* and David Attwell

Department of Neuroscience, Physiology & Pharmacology

University College London, Gower Street, London, WC1E 6BT, UK

Address correspondence to DA, d.attwell@ucl.ac.uk

*Contributed equally

Consider how advantageous it might be to have eyes on our hands, rather than on our faces: depth perception would be improved by the greater distance between the eyes, and it would be easy to look into relatively inaccessible spaces by appropriate movement of the hands. The absence of mammals that use this visual strategy draws attention to constraints on how evolution is able to "design" the nervous system. As discussed below, energy use in particular, in this case the large amount of energy that would be needed to send visual information along the ~10^6 optic nerve axons over the length of the arms to the brain (instead of along the much shorter optic nerve), imposes significant design constraints on the nervous system.

In fact there are remarkable analogies between the constraints operating when designing computer chips and those operating when evolution "designs" nervous systems, including the need to reduce energy use, decrease wiring length, reduce device capacitance and reduce noise. In this Primer, we review how nervous systems are optimised at the molecular, cellular and wiring levels to maximise information processing and transmission in relation to energy used, and consider the trade-offs involved in the evolution of such systems.

Energy

The brain is approximately 2% of the body's mass but consumes ~20% of the body's resting energy production. Anthropologists have suggested that, as primates have evolved, in order for the body to be able to increase its energy use on the brain, increases in the efficiency of the gut (e.g. through the invention of fire and cooking to present food to the body in a more digestible form, and the adoption of a meat eating diet) or of locomotion, have been needed.

Of the energy going to the brain, supplied as oxygen and glucose in the blood, roughly half goes to power excitatory (glutamatergic) synapses, with substantial fractions also being expended on action potential propagation and maintenance of cell resting potentials (Fig. 1). Brain energy use does not change dramatically during sleep (there is only a small, ~15%, decrease during non-REM sleep). The large energy use of the brain implies that energy

supply is a significant constraint on brain function. Within any given brain area, the resting energy supply through the vasculature is insufficient to provide the extra energy needed when neurons become active, in part because increasing the density of blood vessels would take away space that is needed for the neurons themselves and thus decrease information processing power. This requires that neurons and their associated astrocytes release vasodilating agents to increase local blood flow when neuronal activity increases (so-called neurovascular coupling). Indeed, the energy supply to nervous tissue seems precariously close to the limit for maintaining normal function: hypoglycaemia induces a fall of cognitive power, while ingesting a glucose source (but not an artificial sweetener) improves cognitive decisions. This may involve astrocyte-mediated transfer of glucose-derived lactate to neurons, since long-term potentiation of synaptic transmission depends on this transfer.

The large energy expenditure on synapses is mostly employed to pump out of the postsynaptic cell the ions (largely Na^+ and Ca^{2+}) that enter to generate postsynaptic currents and membrane potential depolarisation. Appropriately, synapses are a major site for the release of factors mediating neurovascular coupling. Several molecular and anatomical aspects of synapse evolution seem designed to maximise information transmission per energy used (Fig. 1). First, at least for visual system synapses (from retinal ganglion cell axons to lateral geniculate nucleus (LGN) neurons, and from LGN axons to cortical neurons), the number of postsynaptic glutamate-gated ion channels (AMPA receptors) is adjusted to generate a postsynaptic signal that is large enough to be detected above background noise, but not so large as to evoke unnecessarily large ion influxes that do not significantly increase information flow. Second, the probability of presynaptic vesicle release in response to an action potential is typically very low at central nervous system synapses (~0.2). It may seem inefficient to send an action potential all the way to a presynaptic release site and then not release neurotransmitter but, for central synapses where typically there are ~6 release sites from each presynaptic axon onto a given postsynaptic neuron, it turns out that this low release probability allows a reasonable amount of information to be transmitted

while greatly decreasing the energy expended on ion entry postsynaptically, thus maximising information transmitted per energy used.

Wiring

The hypothetical example of eyes-on-hands proposed above highlights the importance of minimising energy use by minimising the number and length of axons over which information has to be transmitted. The retina provides a well-known example of this: there are ~100 million photoreceptors in the human retina (in order to provide detailed information on the visual world) but only ~1 million optic nerve axons transmit visual information to the brain. This is because the energetic cost (and also the space occupied) would be far higher if every photoreceptor sent an axon to the brain (energy is used both on constructing the axons initially and then on propagating signals over them). Instead, therefore, pre-processing of information in the neuronal cellular layers of the retina is employed to retain only the most useful information for transmission to the brain, thus saving energy.

Similar principles pertain for the arrangement of the white matter "wiring" that connects different grey matter "processing nodes" in the nervous system (Fig. 2). In the nematode nervous system it has been shown that, of ~40 million different possible ways of physically locating the various neuronal ganglia ("processing nodes") and wiring them together, the observed layout minimises wiring length.

It can also be advantageous to trade off the number of axons transmitting information rapidly (which generally implies a larger axon and greater energy use) and slowly (with smaller, less energy-demanding axons). For example pain information is transmitted rapidly from peripheral receptors by myelinated Aδ axons (see below for the signal speeding function of myelin), to allow rapid reflex removal of the body from the pain source, but also transmitted more slowly by smaller unmyelinated C fibre axons, perhaps to give greater spatial resolution of the pain stimulus location with less space occupied in the nerve. Similarly, major white matter tracts like the corpus callosum in mammals contain a mixture of myelinated and unmyelinated axons.

Space

Space, like energy, is a precious resource within the nervous system. At the gross anatomical level, the need to connect neurons with many fast axons has driven evolution to segregate the brain into white matter (fast-transmitting) tracts and grey matter (information processing) regions containing densely interconnected neurons (Fig. 2). Within the grey matter, evolution could, in principle, result in brains with a large number of very small neurons or a smaller number of larger neurons. In addition, the shape of the neurons will dictate the space that they occupy.

In general, smaller neurons will use less energy, because their smaller surface area means that their membrane capacitance is less and so, to change the membrane potential, less ions need to cross the cell membrane (and be pumped out again, using energy). However, there is a limit to how small neurons can be made because smaller neurons have a higher resistance, and the existence of random ion channel openings and closings can lead to excessive background voltage fluctuations that obscure the signal being processed or transmitted. Conversely, larger neurons will use more energy but may be desirable if reliability of signal transmission is crucial, or if a large number of input connections have to be received by the cell, usually distributed over dendritic branches and spines. The cerebellum gives examples of both of these strategies (Fig. 3), where a vast number of granule cells (~50-80 billion in humans) is used to distribute the encoding of (e.g.) sensory and motor information over many cells in order to maximise the information storage underlying movement control (see below for more on distributed coding), while large Purkinje cells with an enormous dendritic arbour are used to process the information arriving at each Purkinje cell on ~200,000 input granule cell axons. The speed required for the neuron's output action potentials may also dictate the soma size: faster (and hence larger) axons may require a larger soma to maintain their biochemistry.

Time

Nervous systems generally operate on a time scale of milliseconds (msec), as assessed by: the duration of action potentials and synaptic currents (~1 msec), membrane time

constants that limit the speed of membrane potential changes evoked by synaptic currents (~10 msec), and the intervals between action potentials when neurons are active (2.5–250 msec). This may reflect the time scale over which interactions with the environment are essential, including processing of incoming sensory information and generation of motor signals to move body parts. However, it is notable that animals with very different visual environments and limb masses, such as insects and mammals, all have neurons that operate on a time scale of msec, which may indicate the existence of common factors that limit neurons of 'standard design' to operating on a msec time scale. Notably, the capacitance of biological membranes formed from standard lipid bilayers and the densities of ion channels normally expressed appear to result in a membrane time constant of ~10 msec, even though the membrane capacitance per area of membrane may be ~2-fold lower in some human neurons.

The msec time scale of operation imposes constraints on numerous molecular and anatomical aspects of brain function. If action potentials repeated at msec intervals are to have distinct effects postsynaptically, then synaptically-released glutamate's postsynaptic actions need to last only a few msec. This is achieved in two ways. First, clearance of glutamate from the synaptic cleft, which occurs largely by diffusion to surrounding regions where uptake carriers maintain a low extracellular glutamate concentration, is achieved on a msec time scale by making synaptic boutons have a small diameter, typically <1 μm. Thus, the time scale of neuronal operation dictates the physical size of synapses (Fig. 4). Secondly, the glutamate receptors mediating fast synaptic transmission (AMPA receptors) have a low affinity so that, when a synapse releases glutamate and its concentration then falls rapidly, the receptor will rapidly lose its bound glutamate and the postsynaptic current will be terminated. Thus, the molecular properties of postsynaptic receptors are also dictated by the time scale of neuronal operation (Fig. 4). Note that not all receptors have a low affinity for such a reason: NMDA receptors, which mediate coincidence detection by sensing both presynaptic glutamate release and postsynaptic depolarisation (which removes Mg^{2+} from their ion channel), have a high affinity in order to stay activated for as long as ~100 msec by

a ~1 msec glutamate transient, to increase the chance that some coincidences of pre- and post-synaptic activity are detected.

Since most brain energy is used on synaptic currents and the action potentials that drive them, it follows that this energy use - and the energy supply needed - will be roughly proportional to the mean firing frequency of neurons. Consequently, if evolution were to produce neuronal firing patterns at (e.g.) a 10-fold higher frequency to increase the temporal resolution of neural information processing, then the blood supply to the brain would have to be increased 10-fold to power this increase in cognitive power.

Time becomes an important constraint when communication is needed between distant parts of the nervous system. For relatively local communication, as can be achieved with passive electrotonic conduction along nerve cell processes, for example along the neurons of the retina or the dendrites of cortical neurons (up to a few 100 microns long), conduction delays are minimal and transmembrane voltage changes decay with distance by a factor which does not lead to excessive contamination by ion channel opening-induced noise. However, the electrical space constant of neuronal processes (the distance over which a passively-propagating voltage decays e-fold) is typically a few 100 microns and so, for communication across the whole brain, passive signals would decay to the extent that they would become indistinguishable from noise. The evolution of regenerative action potentials overcomes this problem, but raises the question of how long it will take to propagate information across the brain.

Action potential speed is limited by the density and conductance of voltage-gated Na^+ channels, but also by the capacitance of the cell membrane, which takes time to be charged by current entering the cell. In addition, a high capacitance implies that more charge (typically Na^+) entry will be needed to change the membrane voltage by the ~100 mV of the action potential, and hence more energy will be needed to pump out these ions again afterwards. A common evolutionary response to this situation is to generate cells (oligodendrocytes in the central nervous system, Schwann cells in the periphery) that wrap axons with many lipid membranes (myelin), thus decreasing the effective cell capacitance

(Fig. 2). As well as speeding the action potential, this also saves space in the nervous system, since to produce an equally fast action potential in an unmyelinated axon would require the axon to be much larger. Nevertheless, although myelin saves energy used on the axon itself, it does not save it for the nervous system as a whole, because the energy expended on growing the myelin sheath and maintaining the resting potential of its oligodendrocyte usually outweighs the energy saved on impulse propagation.

Coding

Information is coded in the nervous system as changes of membrane potential, evoked by neuronal excitation (depolarisation to a more positive intracellular voltage) and inhibition (hyperpolarisation to a more negative voltage, or an increase of cell conductance with no change of voltage). One might imagine that neurons could function solely with excitatory synapses, because the resting potential is an arbitrary level from which voltage displacements are made, but in fact the existence of shunting inhibition (an increase of conductance to ions with a reversal potential close to the resting potential) confers on neurons the ability to carry out operations of multiplication and division, in addition to the addition and subtraction that result from linear summation of excitatory or inhibitory postsynaptic currents with reversal potentials far from the resting potential. Another, energetic, reason for favouring computation with both excitation and inhibition is that inhibition may allow information to be represented with less energy use, because inhibition can alter the membrane potential without the large influx of Na^+ ions (that must then be pumped out, consuming energy) which is needed for excitatory synapses.

The majority (~85%) of synapses in the brain are excitatory. However, the regulation of neuronal excitability by inhibition is crucial, not only to prevent hyperexcitability and seizure generation, but also to control the range of summed excitatory input strengths that can generate functionally different outputs from the cell, i.e. to match the coding range of the cell to the range of incoming input strengths. Commonly, a neuron receiving direct excitation from an axon originating in another brain region will also receive disynaptic inhibition driven by that same axon exciting an inhibitory interneuron (Fig. 4). This has the effect that, when

the amount of excitation entering an area is increased, the amount of inhibition occurring increases too, which expands the range of afferent input strengths that neuronal populations can represent.

The common neural circuitry motif of an input evoking direct excitation followed by delayed inhibition also confers a greater sensitivity to changing signals than to maintained signals - a coding strategy that is common throughout the nervous system which, although it removes an exact measure of the incoming signal, serves both to save energy and to extend the useful coding range of cells. For example, when we pull our clothes on in the morning, we feel them going on, but we are not usually bothered by a persistent signal telling us that the clothes are on. This reflects an energy-saving adaptation in the sensory signal transmitting the fact that the clothes are present, which often starts right at the level of the sensory receptor itself, but also occurs at higher levels of the neural circuitry.

A further strategy employing inhibition that has evolved to reduce energy use, and maximise matching of the response range of neurons to the natural range of signals they are representing, is predictive coding, in which the most probable value of a response is subtracted from the actual value. Again this removes an exact measure of the incoming signal, but maximises the response size for unexpected signals, which are the most useful ones for the brain to know about. A good example is the excitatory centre - inhibitory surround organisation of the receptive field of retinal neurons, in which the average light intensity over a large area around the cell is subtracted from the value occurring in a smaller area centred on the cell. The size of the inhibitory surround can then be varied according to light level (which alters the amount of photon noise present), to optimise the amount of inhibition according to the reliability of the predicted central signal.

For some circuits it is important to have one or a few cells uniquely coding information related to one conceptual object (for example motoneurons projecting to one particular muscle). However, in other circuits, information related to one conceptual object (or context) is often distributed over a larger number of neurons, with the excitation of different combinations of neurons representing a distinct concept (individual neurons each participate

in the coding of a few concepts, and each concept is coded by a small fraction of neurons). This decreases the number of neurons needed to encode different ‘concepts’ or sets of sensory and motor data, and thus reduces their energy use. The classic example of this sparse distributed coding is in the cerebellum, where sensorimotor context arriving on afferent axons is recoded into the activity of the large number of granule cells, a weighted sum of whose activity is then computed by Purkinje cells to modulate motor output (Fig. 3).

Glia and energy supply

Apart from neurons, glia play crucial roles in the nervous system, and they tend to be found in higher numbers in species and brain regions that have larger neurons. As detailed above, oligodendrocytes and Schwann cells speed action potential conduction, while astrocytes regulate the ion composition of the extracellular space, take up released neurotransmitters to terminate synaptic transmission, and regulate the development of synapses on neurons. These cells probably also play another key role in providing energy to active neurons. This may be particularly important for long myelinated axons, most of the volume of which is cut off from the glucose in the extracellular space by the myelin around the axon. It is suggested that glucose is taken up into oligodendrocytes, and then provided to the neuronal axon (perhaps as lactate) at the inner surface of the myelin. Similarly astrocytes, which have endfeet processes close to capillaries and are thus well placed to take up glucose delivered in the blood, may deliver lactate to neurons, at least under some circumstances. In both cases the lactate thus provided will be converted to pyruvate which can be used to power neuronal mitochondria.

Conclusion

This Primer has emphasised the compromises made by the nervous system to reduce energy use while maintaining as useful as possible a representation of signals being processed. It is interesting that, for similarly energy-limited applications, the design of computer chips also employs similar strategies, such as removing connections within integrated circuits in order to reduce energy expenditure more than it reduces information processing power.

It is intriguing to consider how the nervous system senses energy expenditure and compares it with available energy supply, in order to optimise information processing in pathological states when the energy supply is decreased. In the short term, metabolic signals such as a fall of intracellular ATP level (which opens K^+ channels) and a rise of extracellular adenosine level (which suppresses glutamate release) may play important roles in this adaptation. In long term states of lowered energy supply, altered trafficking of synaptic receptors and vesicles, and the HIF (hypoxia-inducible factor) pathway, are attractive subjects for further study of the energetic optimisation of CNS function.

Further Reading

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Figure Legends

Figure 1. Optimisation of energy use by neurons. Energy is supplied to the brain as oxygen and glucose in the blood. Inset: Most energy (in the form of ATP) is used on: (i) ion pumping to restore ion gradients postsynaptically at excitatory synapses after ion entry via AMPA and NMDA receptors, and Ca^{2+} release from internal stores; (ii) presynaptically after Ca^{2+} entry to trigger vesicle release, pumping of neurotransmitter into vesicles, and also on the vesicle cycle; (iii) in axons after action potentials (APs); (iv) in astrocytes to power the glutamate-glutamine cycle; and in all cells to maintain (v) their resting potentials (RPs) and (vi) housekeeping activities such as protein and lipid synthesis. The probability of presynaptic vesicle release ($P_{release}$) when an action potential arrives and the number of postsynaptic receptors are key determinants of synaptic energy use, raising the question of how they are optimised. Presynaptically, the combination of ~6 release sites from any one axon onto a postsynaptic cell (in the cerebral cortex) and a low vesicle release probability at each release site has been shown to maximise the amount of information transmitted per ATP used on postsynaptic ion entry. Postsynaptically, for some visual system synapses, the number of AMPA receptors has been shown to be set so as to maximise the amount of information transmitted per ATP used to restore ion gradients after synaptic transmission occurs. Figure made with BioRender.com.

Figure 2. Wiring optimisation. (A) The total length of axons ("wires") in the nervous system is reduced if the tissue is segregated into grey matter processing nodes (PNs, arbitrarily numbered 1-4 here) where neurons are densely interconnected by short axons, and white matter "information superhighways" transmitting information rapidly between grey matter nodes via myelinated axons (and more slowly via unmyelinated axons). In addition, processing nodes dealing with related information should be located closer together than those dealing with unrelated information, to minimise the wiring length (and hence energy use) needed to connect areas. (B) Example of white matter tract in the brain: the corpus callosum (pale white tract running roughly horizontally) linking the grey matter (GM) "processing nodes" of the two cerebral hemispheres (PNs are numbered arbitrarily, one

neuron [blue] passing through the white matter is shown). Inset below shows a myelinated axon, comprised of an axon that is mainly wrapped with membranes forming the myelin, apart from a non-wrapped short segment (the node of Ranvier) where voltage-gated Na^+ channels (Nav) regenerate the action potential. Inset to right is a highly simplified schematic of the wiring of a cortical column in the grey matter (filled triangle at line ends indicate excitatory synapses; flat line ends indicate inhibitory synapses). Figure made with BioRender.com.

Figure 3. Use of space by neurons. The cerebellar cortex, of which only part of the wiring is shown here, contains both the brain's smallest and largest neurons. Sensorimotor and other information is distributed over a very large number of tiny granule cells, with each input (mossy fibre) axon synapsing onto ~500 granule cells. Each granule cell takes part in representing many sensorimotor and cognitive contexts. The output axons of about 200,000 granule cells synapse onto the extensive denditic tree of each very large Purkinje cell output neuron, which sends a single axon to the deep cerebellar nuclei to modulate e.g. the body's motor output. Figure made with BioRender.com.

Figure 4. Factors shaping neuronal responses. (A) Schematic showing a microcircuit in which an axonal input activates an excitatory synapse onto an output cell. Release of glutamate into the synaptic cleft evokes a brief transient of the concentration of glutamate, which diffuses out of the cleft in ~1 msec to surrounding regions where astrocyte glutamate transporters maintain the concentration at a low level (1). This transiently activates low affinity AMPA receptors to generate an inward current lasting a few msec, and high affinity NMDA receptors to generate a current (provided depolarization by another input has removed Mg^{2+} from the receptor channel) that lasts ~100 msec (2). The axonal input also activates an inhibitory interneuron which inhibits the postsynaptic output cell with a delay after the excitation arrives, so that during a train of input action potentials the response of the output cell is larger when the input increases than when it is maintained, reducing long-term energy use. (B) Predictive coding. Three inputs carrying (for example) sensory inputs from 3 adjacent locations along a sensory dimension (such as position on the retina or skin) project

to 3 output neurons. In addition the 3 inputs excite an inhibitory interneuron that computes the most likely value of the signal at the central input cell. This is then subtracted from the central output, which as a result encodes only deviations from the expected signal, saving energy and increasing the coding range devoted to unexpected signals. Figure made with BioRender.com.

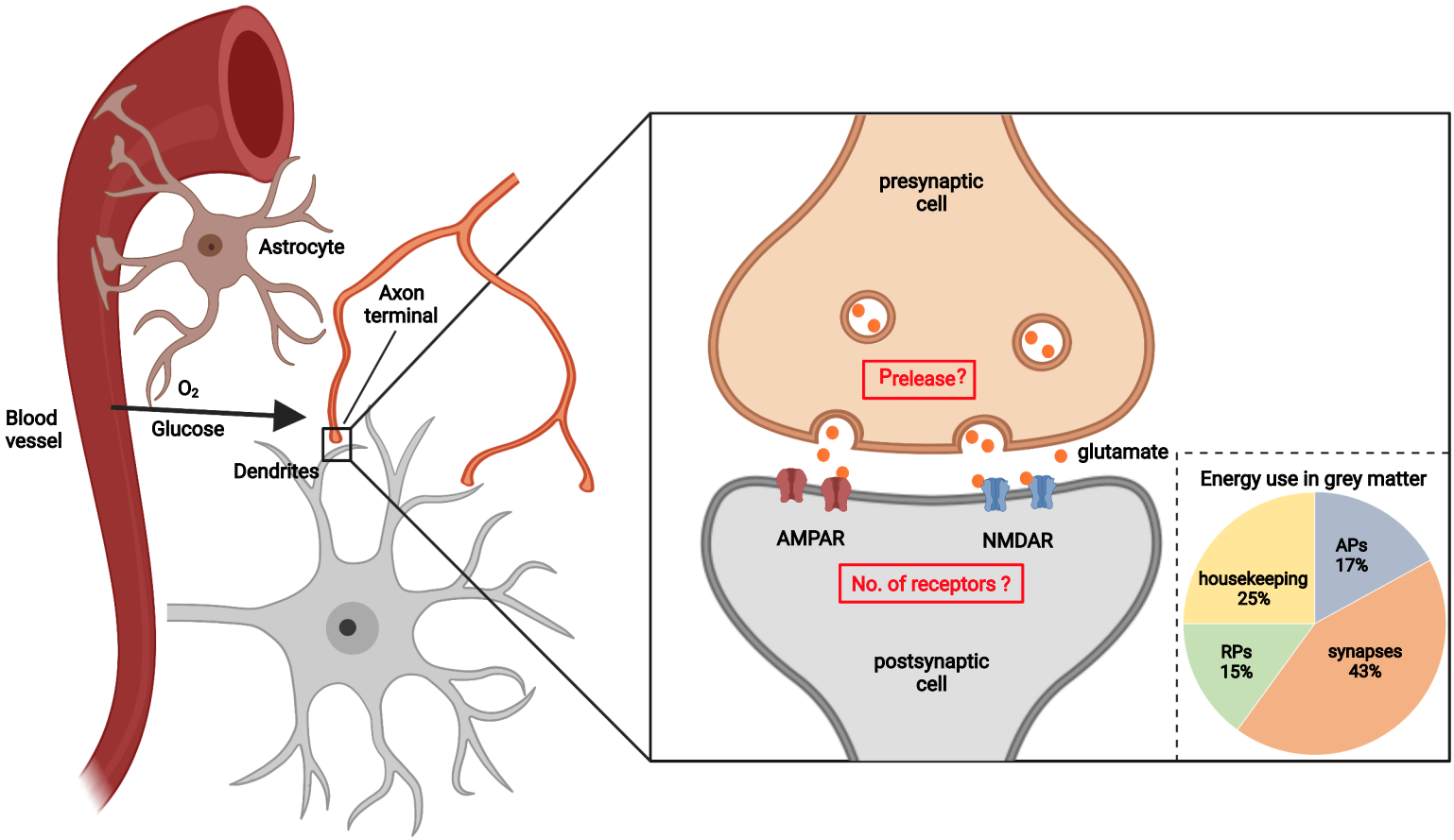

Astrocyte
Axon terminal
Blood vessel
O_2
Glucose
Dendrites
presynaptic cell
Prelease?
glutamate
AMPAR
NMDAR
No. of receptors ?
postsynaptic cell
Energy use in grey matter
APs 17%
housekeeping 25%
RPs 15%
synapses 43%

Figure 1

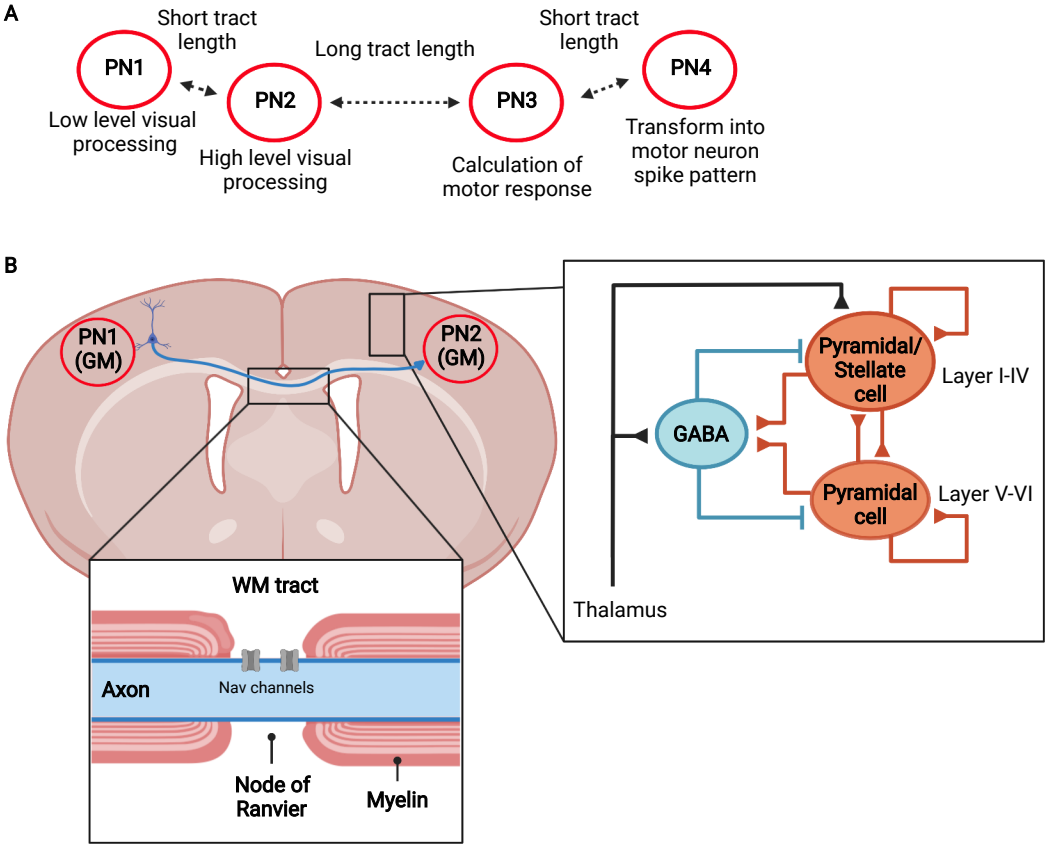
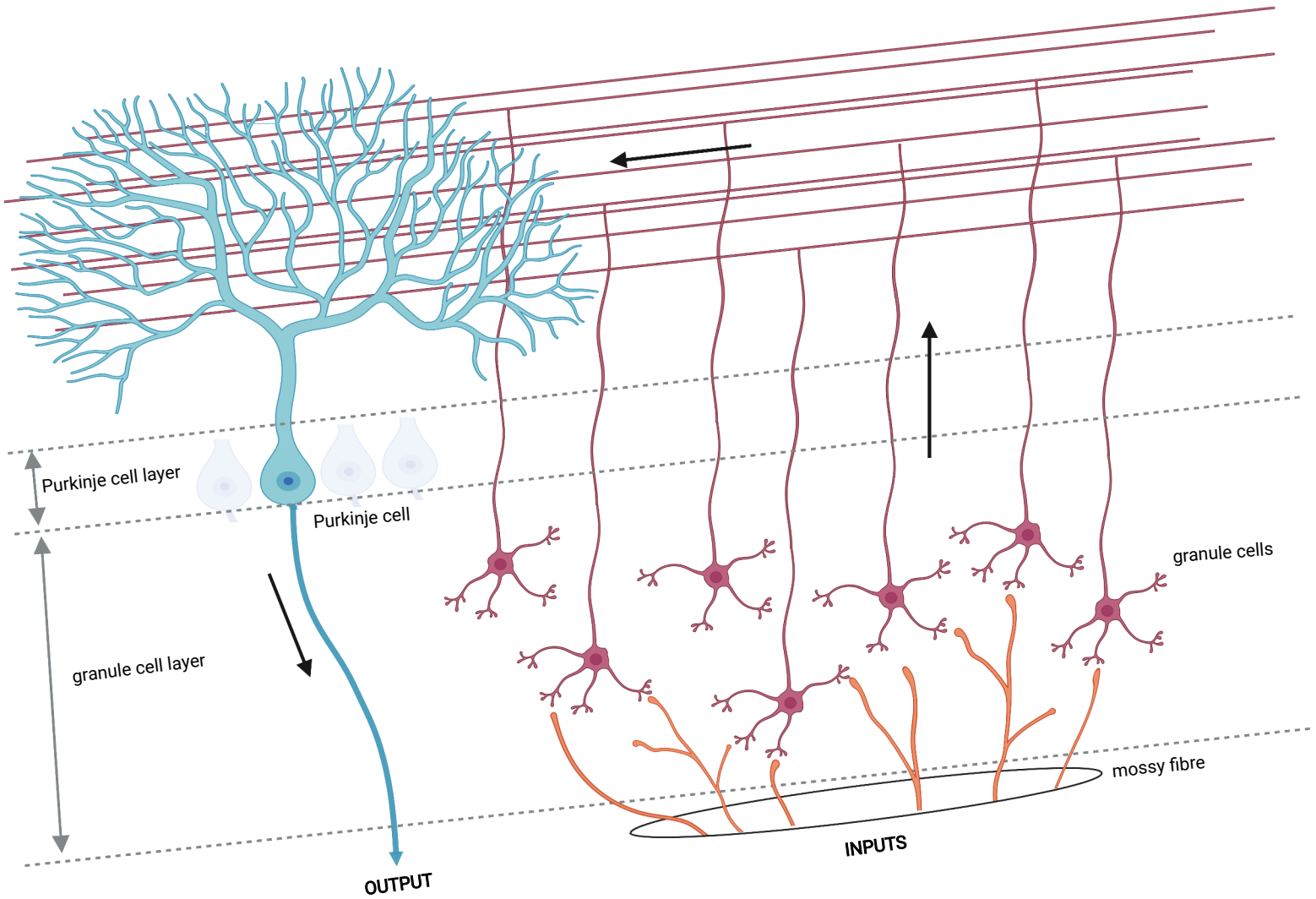

A
PN1
Short tract length
Low level visual processing
PN2
Long tract length
High level visual processing
PN3
Short tract length
Calculation of motor response
PN4
Transform into motor neuron spike pattern
B
PN1 (GM)
PN2 (GM)
WM tract
Axon
Nav channels
Node of Ranvier
Myelin
Pyramidal/ Stellate cell
Layer I-IV
GABA
Pyramidal cell
Layer V-VI
Thalamus

Figure 2



Purkinje cell (large)

- 200,000 input synapses
- mediate complex computations
- large area and energy use

Granule cells (small)

- ~ 4 input synapses
- remap input information over a large number of cells
- small area and energy use

Figure 3

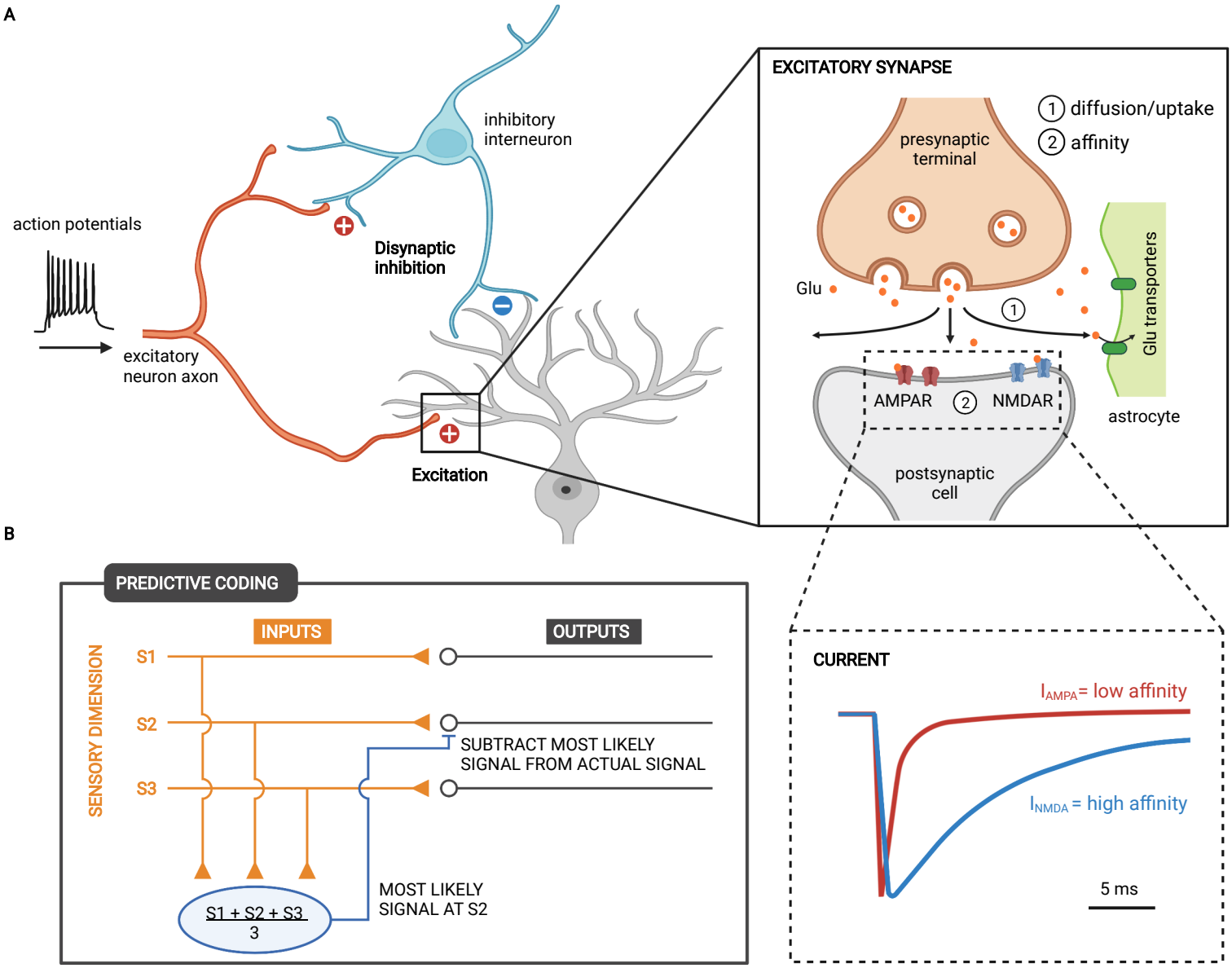

A
action potentials
excitatory neuron axon
inhibitory interneuron
Disynaptic inhibition
Excitation
EXCITATORY SYNAPSE
presynaptic terminal
1 diffusion/uptake
2 affinity
Glu
Glu transporters
AMPAR
2
NMDAR
astrocyte
postsynaptic cell
B
PREDICTIVE CODING
INPUTS
OUTPUTS
SENSORY DIMENSION
S1
S2
S3
SUBTRACT MOST LIKELY SIGNAL FROM ACTUAL SIGNAL
S1 + S2 + S3 / 3
MOST LIKELY SIGNAL AT S2
CURRENT
I_AMPA = low affinity
I_NMDA = high affinity
5 ms

Figure 4