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Synaptic Pathways in Neural Microcircuits

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Abstract: The functions performed by different neural microcircuits depend on the anatomical and physiological properties of the various synaptic pathways connecting neurons. Neural microcircuits across various species and brain regions are similar in terms of the repertoire of neurotransmitters, synaptic kinetics, short- and long-term plasticity, and target-specificity of synaptic connections within the microcircuit. Microcircuits can however be fundamentally different in terms of the precise recurrent design used to achieve a specific functionality. In this review we compare the connectivity designs in the spinal cord, hippocampal, neocortical and cerebellar microcircuits, and discuss the different computational challenges that each microcircuit faces.

Introduction

Neural microcircuits are fascinating because they generate a "life of their own". These emergent states take on many different forms depending on the cellular and synaptic design of the microcircuit. Microcircuits are similar in that they use excitatory and inhibitory neurons interconnected with dynamic synapses to embed inherited information on how to execute specific behaviours. A specific microcircuit is also surprisingly similar across different species. Microcircuits can be constructed to produce autonomous rhythmic behaviour (spinal cord), sequential relays and transformations of information to build maps of associations between parameters of the world (hippocampus), predict events and deal with real-time updates (neocortex), or compute error functions of the mismatch between the predicted and the actual world (cerebellum). In this review, the basic designs of the lamprey spinal cord microcircuit, the hippocampal, neocortical and cerebellar microcircuits are presented in a highly condensed form. The aim is not to cover comprehensively the microcircuits of each of these brain regions, but to give a flavour of the differences and similarities in the microcircuit designs. The computational challenges that each microcircuit faces are also discussed.

Synaptic Transmission in the spinal locomotor network

In all vertebrates, locomotion is coordinated by spinal networks referred to as central pattern generators (CPGs) (for a recent review, see Grillner 2003 [1]). We will use the synaptic interaction within the lamprey CPG as the model system, since it is currently the best understood adult network, but important information is also available from the developing nervous systems of amphibians and rodents [2,3]. The spinal networks consist of motoneurons (MN) and various types of interneurons (see [1,4-11]). The MNs receive inputs from ipsilateral excitatory interneurons (EINs) using glutamate, and are inhibited by glycinergic commissural neurons (CC) with their cellbodies located on the contralateral side (**Fig. 1**). The EINs are responsible for burst generation, while the periodic contra-lateral inhibition is responsible for alternating the burst activity between antagonist MN groups. The locomotor CPGs are turned on by glutamatergic reticulospinal commands from the brainstem (see Grillner et al., this volume).

The core burst generating microcircuit is formed by a population of EINs, which can generate bursts even when inhibitory synaptic transmission is blocked. The intrinsic properties of these neurons ascertain burst termination [5,12-14]. The EINs use

both AMPA and NMDA receptor activation to recurrently excite each other as well as the motoneurons, and typically produce unitary EPSPs of around 1 mV (see [1,8,15,16]). Synapses differ in their activity dependence, some become depressed during continuous activity, whereas others instead become facilitated. This property is clearly of importance within a network, as established both in the spinal cord and neocortex (see below). The EIN to EIN synaptic connection displays synaptic depression during high frequency activity in some but not all cases (**Fig. 1a,** [8]). Some, but not all of the EIN synapses onto the CCs display pronounced depression but others facilitation (**Fig. 1f** [7]). The EIN synapse onto the motoneurons is also depressing in about 50% of the cases (Parker and Grillner 1999, Parker 2003). While bursts can be terminated by inhibition from CCs, the EINs also contains ion channels that are capable of terminating burst activity, such as Ca^{2+} dependent K^{+} channels [12,17,18]. With regard to other premotor interneurones, the contralateral glutamatergic EPSPs from small commissural interneurons (EScINs) show marked depression (**Fig. 1e**), while some of the small commissural inhibitory interneurons (IScIN) facilitation (**Fig. 1d**). When considering the synaptic transmission, within the network, the activity dependence is thus an important consideration.

The degree of activity-dependent depression itself is subject to modulation by 5-HT and substance P [7]. Substance P facilitates ipsi-lateral excitation (**Fig. 1b**), and reduces contra-lateral inhibition by facilitating the depression of the inhibitory input (reducing net-inhibition), which enhances the burst frequency. 5-HT instead has the opposite effect of sustaining the inhibition (enhances net-inhibition), and hence lowering the burst frequency. This process is referred to as a meta-modulation, since a transmitter modulates the degree of activity-dependence of the synapses [7]. These effects contribute to the burst frequency modulation elicited by these two modulators, together with their effects on somatodendritic level (see [1,19]). For the EIN synapse onto motoneurons, there is also a marked facilitating meta-modulation by 5-HT, which will increase the response of the motoneurons to a given level of activity in the spinal cord microcircuit [7].

Although inhibition is not essential for burst generation, there is an additional type of inhibitory interneuron (ISiIN), which receives input from the locomotor CPG, and the EINs [6,8]. It inhibits ipsilateral motoneurons with a depressing synapse (**Fig. 1c**), and inhibits ipsilateral CCs with a facilitating synapse (**Fig 1g**). A possible role

for this synaptic pathway is to turn off the contralateral inhibition, which allows the contra-lateral microcircuit to initiate its activity phase.

By recording from the presynaptic terminals of both excitatory and inhibitory interneurons during ongoing fictive locomotion, it was further shown that the presynaptic terminals are phasically inhibited by GABAergic modulation mediated by GABA interneurons acting on both $GABA_A$ and $GABA_B$ receptors [20-22]. This phasic presynaptic inhibition is maximal during ipsilateral activity in both synapses. While the presynaptic inhibition of burst activity may seem logical, the depression of ipsilateral EINs during a burst may seem counterintuitive. Tuning the efficacy of the EIN to motoneuron synapse, may however provide an additional mechanism to optimize network function. Sensory afferents also receive phasic presynaptic GABAergic modulation, whereas the descending reticulospinal command fibres are not subject to this type of modulation. In addition to the phasic, CPG induced modulation, several modulators provide a tonic regulation of synaptic efficacy such as the different metabotropic glutamate receptors (class II-III), $mGluR_1$ triggered endocannabinoids, dopamine, 5-HT, neuropeptides like NPY, CCK and substance P [7,23-25]. There are thus rich possibilities to fine tune the different synapses by the different modulator systems (see LeBeau et al., this volume).

In conclusion, the spinal cord pattern generation depends for the fast synaptic interaction exclusively on glutamatergic and glycinergic synaptic transmission, although there is a rich repertoire of slow modulatory effects. This basic network can, thus, be fine tuned by a number of different aminergic or peptidergic transmitters that target different pre- or postsynaptic mechanisms within the microcircuit. This provides possibilities to modify the segmental output at a given supraspinal drive, and the intersegmental coordination.

Synaptic Transmission in the Hippocampus

The hippocampus can be subdivided into CA3, CA2 and CA1 subfields and several excellent reviews describe the circuitry in detail [26,27]. A simplified circuit diagram showing some of the major synaptic connections in the hippocampus is illustrated in (**Fig. 2**; see also Grillner et al., this issue).

Several excitatory to excitatory (E-E) connections exists in the hippocampus with information processed by the dentate gyrus projected to CA3 pyramidal cells via the mossy fibers and these pyramidal cells then project their output to CA1 pyramidal

cells via the Schaffer collateral pathway. However, this can no longer be viewed as a simple trisynaptic excitatory loop for reasons discussed below. CA3 pyramidal neurons receive extrinsic perisomatic excitation near their somata from the large mossy terminals of granule cells of the dentate gyrus which display brief synaptic facilitation (**Fig. 2g**)[28]. Intrinsic E-E connections arise from local axon collaterals of CA3 pyramidal cells and there is a highly divergent connection from CA3 to CA1 where one CA3 pyramidal cell contacts 30-60,000 other pyramidal cells, mostly in CA1 [29]. Paired recordings of CA3 to CA1 pyramidal cells showed small amplitude (mean 0.13 mV) unitary EPSPs [30]. The large degree of divergence from CA3 to CA1 favours rapid synchronization of the CA1 population. CA1 pyramidal cells seem to be even less interconnected than CA3 and paired recordings reveal larger EPSPs (mean 0.7 mV) that display synaptic depression **(Fig. 2d)** [31].

In addition to chemical synaptic signalling, electrical signalling via gap junctions has also been observed experimentally between pyramidal cells [32,33]. Based on experimental and modelling data it has been proposed that gap junctions between pyramidal cells may be axo-axonic [34] and such electrical coupling appears to be required for both gamma frequency and ultra-fast oscillations [34].

Excitatory to inhibitory (E-I) connections produce the feedback and feedforward inhibitory circuits in the hippocampus. An important feature of E-I transmission is that EPSPs recorded in interneurons are generally faster than those in pyramidal cells. Granule cell synapses on to the basal dendrites of basket cells in CA3, generate EPSCs with very fast kinetics (half duration ~ 4 ms) due to rapid AMPA receptor deactivation [35]. Fast EPSPs in interneurons allows for the precision of spike timing that is important for inhibition-based rhythms such as gamma frequency activity [34]. In the mossy fibre pathway approximately 10 times more synaptic contacts are in fact formed onto interneurons in CA3 than onto pyramidal cells [36], and the probability of release, and quantal amplitude is higher at these MF-interneuron synapses than at MF-pyramidal cell synapses (see Lawrence and McBain for review[37]). This generates a substantial inhibitory feedforward signal where the net effect MF activation on CA3 pyramidal cells is in fact inhibitory thus complicating the original view of a simple trisynaptic excitatory loop. However, at higher frequencies (>20Hz) there is a shift to a net excitatory drive due to facilitation of E-E and depression of E-I connectivity [38]. Interneurons in the CA1 receive mostly feedforward excitation from Schaffer collaterals [39]. Local connections between

pyramidal cells and interneurons gives rise to a strong recurrent inhibition, in that action potentials in pyramidal cells frequently evoke IPSPs in neighbouring pyramidal cells. Paired pyramidal-interneuron recordings in CA3 show that the probability of spike transmission is high (a probability as high as 0.6) with mean EPSP amplitudes in interneurons being between 0.2 and 4 mV, often involving only a single release site [40,41]. Similar values have been reported for the CA1 areas [42-44]. At least three classes of interneuron receive excitatory axon collateral inputs from the pyramidal cells; basket cells, bistratified cells and O-LM cells [41-44]. These E-I connections show important differences in terms of frequency dependent depression or facilitation of the postsynaptic response occurs. Upon repetitive activation, unitary pyramidal cell inputs onto CA1 basket cells and bistratified cells **(Fig. 2b)** show a gradual depression of their amplitudes while those onto O-LM cells **(Fig. 2c)** strongly facilitate[42,43]. Although, there is in fact considerable variability in short-term plasticity, even within an interneuron class [45].

Inhibitory connections onto pyramidal neurons have been broadly divided into those interneurons that provide perisomatic inhibition e.g. basket cells, axo-axonic and bistratified cells [41,44,46] and those that provide inhibition to more distal dendritic regions e.g. O-LM cells [43]. Recently Pouille and Scanziani [39] demonstrated how several key features of synaptic transmission, when incorporated into the feedback inhibitory circuit, could shift recurrent inhibition from interneurons that targeted pyramidal cell somas, to dendrite-targeting interneurons. They showed that during a train of action potentials in pyramidal cells, the onset of the stimulus elicited spikes with little delay in the so-called "onset-transient" interneurons that were perisomatic targetting interneurons, i.e. presumed basket-cells, axo-axonic and bistratified cells. In contrast, the later spikes in a train activated the so-called "late-persistent" interneurons that contacted the pyramidal cells dendrites, i.e. presumed O-LM cells. These two recurrent inhibitory circuits were, therefore, proposed to operate as coincidence detectors and integrators respectively. Unitary IPSPs produced by dendritic inhibition tend to be slower than perisomatic IPSPs **(Fig. 2a,e)** [39,47] and it has been shown that dendritic inhibition is effective in suppressing calcium dependent spikes, while somatic inhibition can inhibit action potential discharge [47]. As with E-I connections (above) the I-E connections also exhibit activity-dependent short-term plasticity **(Fig. 2e)**[46].

Intrinsic I-I connections arise from interneurons such as basket cells **(Fig. 2f)** that contact up to 60 other parvalbumin positive interneurons or from interneurons that specifically target only other interneurons [26,27]. Reciprocally connected interneurons are important for synchronising neuronal firing. In addition, gap junctions have been observed between interneuron dendrites in the hippocampus [48], particularly in basket cells, where they form a dense interconnected interneuronal plexus. Such chemically and electrically coupled interneuronal networks are important for theta and gamma frequency oscillations [34].

Synaptic Transmission in the Neocortex

The neocortex is composed of 6 layers, with interneurons in all layers, pyramidal cells (PCs) in layers 2-6 (L2-6) and spiny stellate cells (SSCs) in L4 of primary sensory cortices. PCs, like in the hippocampus, are the principal cells of the neocortex, and are excitatory glutamatergic neurons comprising about 80% of the neurons.

Thalamic input enters primarily into L4 - the first station of sensory processing - targeting SSCs [49] as well as other neurons and dendrites of neurons that pass through L4 [50]. The synaptic input from thalamus seems to be formed by depressing glutamatergic synapses [51,52]. SSCs form a recurrent microcircuit within L4 and also excite L4 PCs using depressing glutamatergic synapses [53]. These PCs are interconnected with depressing synapses (**Fig. 3h**) [54]. SSCs project to pyramidal neurons in L3 via depressing synapses [55] – the second station of columnar processing. L3 PCs are heavily interconnected with a probability of around 0.3 to form a strong recurrent mirocircuit. L3 PCs project to PCs in L2 and both L2 and L3 receive input and provide output to associational brain regions. L2/3 also provides a prevalent descending projection to L5 PCs using depressing synapses [56] – the 3rd station of columnar processing. L5 PCs are also interconnected with depressing synapses but with a lower (around 0.1) probability of interconnections that in L2/3 (**Fig. 3d**) [57,58]. Excitatory connections have also been described between L4 SSCs and PCs in L5 [59,60].

There are two major classes of L5 PCs; the thick tufted PCs which project to sub-cortical regions and provide the major source of output from the neocortex and the thin untufted PCs which project to the contra-lateral hemispheres [50,61]. The L5 PCs also project down to L6 PCs – the 4th station of columnar processing - which are composed of at least 2 major classes of PCs; the cortico-thalamic and the cortico-

cortical PCs. The cortico-cortico L6 PCs project to other neocortical regions in the same hemisphere while the cortic-thalamic L6 PCs are part of a positive feedback loop between the neocortical column and the thalamus – they excite thalamus to amplify input to L4. L6 PCs are also interconnected with depressing synapses (**Fig. 3e**) [62], but some facilitation has been observed in this layer [63-65]. While the largest columnar projection from L6 is back to L4 [66], L6 also provides some feedback excitation to the L5 PCs (**Fig. 3f**) [62]. Thalamic stimulation can generate, what is known as an augmenting response, mostly in the deeper output layers 5 and 6 [67], which may be due to this positive feedback loop between the neocortex and thalamus.

Many pyramidal cells (not all) project their dendrites to L1 to produce the "tuft dendrites". This fan of dendrites, which is electrically quite remote from the somata, is subject to feedback excitation from ipsilateral cortical regions that are related to integration with processing in this particular brain region. For example, in L1 in the primary somatosensory cortex gets feedback from primary motor cortex to L1 [68]. L1 also gets input from the non-specific thalamus [69]. The tuft dendrites receive inhibition from local small interneurons (horizontal cells and Cajal Retzius cells), but probably mostly by the ascending axons of Martinotti cells [70].

Interneurons in the neocortex are composed of different types, differing in their morphological, electrophysiological, molecular and synaptic properties [71]. They can be divided into 4 functional classes: a) those that target the distal dendrites (Martinotti cells) which are analogous to the OLM cells in the hippocampus; b) those that target the mid-range and proximal dendrites (Bitufted, Double Bouquet, Bipolar, and Neurogliaform cells); c) those that also tend to target somata and peri-somatic dendrites (Large, Nest and Small Basket Cells); d) and those that target the axon initial segment (Chandelier cells) [71]. Pyramidal neurons use a spectrum of dynamic synapses to activate interneurons ranging from powerful depressing to powerful facilitation [65,72,73]. Of particular note is the strong facilitation onto Martinottii cells (**Fig. 3c**) [74] (also seen in the connection between PCs and OLM cells in the hippocampus, see **Fig. 2c**) and mostly depression on to the other interneurons, even Bipolar cells (**Fig. 3a**)[75]. Basket cells typically receive depressing synapses, but facilitation has also been observed (**Fig. 3g**) [76]. Taken together this forms an excitatory to inhibitory dynamics map for recruiting interneurons.

Interneurons provide an equally diverse spectrum of depressing and facilitating synapses back onto PCs [77]. Depression still dominates the overall

phenomenon of synaptic dynamics, yet it is less pronounced at inhibitory synapses [78] due to simultaneous facilitation processes at these synapses [77]. Powerful facilitating inhibitory synapses are also produced by some types of basket cells, which can even block high frequency spike discharge (**Fig. 3b**). Interneurons of the same types are interconnected with electrical synapses (for a recent review, see [79]), suggesting that the different types are differentially activated during cortical processing.

All PCs, except those in L4, tend to project laterally crossing columns to excite neighbouring columns. Neighbouring columns are inhibited mostly by two types of interneurons; a) the basket cells that provide lateral inhibition directly across in the same layer that the cell body is located, and b) the Martinotti cells that send an axon up into L1 to project horizontally across several columns [70].

Synaptic Transmission in the Cerebellum

The cerebellum is faced with the problem of processing information conveyed by an immense number of input fibers (estimated at ~40 million in humans) in such a manner that the processed signal can be transmitted over output fibres less numerous by a factor of 40. This task conceivably requires a neuron type able to receive a myriad of synapses (the Purkinje cell), a preprocessing of the input, and a learning mechanism enabling to distinguish input patterns worth of being processed and transmitted from those that can be neglected without harm.

Synaptic transmission in the cerebellum is overall fast, reliable and plastic (for reviews, see [80,81]). The input from mossy fibers, many of which are terminal axons of pathways counting among the fastest of the nervous system, reaches the principal cortical neuron, the Purkinje cell, invariably over two synapses (**Fig. 4**). At the first synaptic stage, located in glomeruli, granule cells act as coincidence detectors of quanta released by mossy fibers (**Fig. 4g**) [82,83]. NMDARs and spill-over of glutamate enhance the reliability of this connection. Spill-over GABA (released into the glomerulus by Golgi cell axons) activates $GABA_B$Rs on the presynaptic mossy fiber and modulates the gain of the postsynaptic granule cells by tonically activating their extrasynaptic $GABA_A$Rs (which generate more than 90% of the chloride current in adult granule cells, [84,85]). Golgi cells are well positioned to gate this input stage. They produce in response to peripheral stimulation spikes with a latency as short as 5 ms (**Fig. 4h**)[86] that evoke phasic IPSCs in granule cells (**Fig. 4j**)[84]. This fast Golgi-cell

response typically is followed by a silent period lasting up to 100 ms (**Fig. 4h**)[81,86] during which granule cells are partly disinhibited.

The activity of granule cells, which constitute the largest neuron population of the brain, presumably is a sparse-coded representation of the mossy-fiber input that can be easier discriminated by Purkinje cells. The second stage, the granule-Purkinje cell synapse (**Fig. 4 a,b**), likewise has a high release probability, although most of the estimated number of 200,000 synapses on a rat Purkinje cell are silent [87]. An as yet unresolved issue is the difficulty to reveal, by peripheral stimulation, any effect of this massive parallel-fiber input, so that the receptive fields of Purkinje cells tend to be much smaller than those of Golgi cells [86] (See also Grillner et al., this issue).

Interneurons of the molecular layer can fire upon single appropriately timed EPSCs [88](**Fig. 4l**). As a consequence of this quantal sensitivity of interneurons, EPSCs in a Purkinje cell are followed by an IPSC that greatly narrows their window for temporal summation (**Fig. 4c,k**) [89]. This is important because the orthogonal orientation of the planar Purkinje cell dendrite onto the axis of traversing parallel fibers has inspired theories proposing that Purkinje cells are involved in timing, by reading out the subsets of active parallel fibers. Interneurons are interconnected through both GABAergic and electrical synapses, and their synchronization might enable a Purkinje cell to fire more precisely, despite its massive dendritic tree. As Purkinje cells are GABAergic neurons with a high spontaneous activity, interneurons disinhibit downstream neurons in the nuclei [80,90,91] (**Fig. 4e,f**).

The hundreds of synapses made on a Purkinje cell by its single climbing fiber constitute one of the most reliable nervous connections. The large Ca^{2+} signal it evokes (**Fig. 4d**) heterosynaptically controls the strength of active parallel-fiber synapses, which can be depressed (LTD) or potentiated (LTP) depending on the postsynaptic Ca^{2+} level: a small increase induces LTP, a large increase LTD [81,92]. Actually, the active search for synapses involved in motor learning has revealed bidirectional plasticity at most cerebellar connections, including the inhibitory Purkinje-cell synapse on nuclear neurons [93]. Through a Ca^{2+}-dependent retrograde release of endocannabinoids, Purkinje cells also induce a short-term depression of their afferent synapses [94].

Finally, the presumed involvement of the cerebellum in timing and motor control raises the question as to how this circuit lacking recurrent excitatory connections is able to produce delays greater than 10 ms (which is the maximum

delay generated by spike propagation along a parallel fiber). Among candidate mechanisms for delayed or sustained response generation are the activation of mGluRs [81], reciprocal inhibition between neurons with a high spontaneous activity, and oscillations [95]. Neurons in the inferior olive [80], granule cells [96] and presumably the 5-HT sensitive Lugaro cells [97,98] are intrinsic oscillators, whereas network oscillations may be generated by the many recurrent connections, including the poorly characterized synapses from recurrent branches of the Purkinje cell axons [95].

Speculations

The spinal cord, hippocampal, neocortical and cerebellar microcircuits are common in that they all rely on interactions between excitatory and inhibitory neurons to perform computations, all use glutamate for excitation and most use GABA for inhibition (except in the spinal cord locomotor microcircuit, where glycine is used), and the synapses all display variable degrees of synaptic dynamics. These microcircuits are however fundamentally different in many respects. The spinal cord relies on a network of excitatory neurons to generate the rhythmic bursts and inhibition that is projected to the contra-lateral sides to alternate bursts. The hippocampus is composed of similar neurons as in the neocortex, but is arranged according to a relay-like design with minimal excitatory recurrent processing at each relay station and where inhibitory interneurons principally orchestrate pyramidal activity. The neocortex on the other hand, is composed of a column of cells organized into several layers of powerful excitatory recurrent microcircuits, each layer connecting to different brain regions. The cerebellum is strikingly different from all the other microcircuits containing a unique inhibitory interneuron that is perhaps one of the most elaborate neurons in the brain and that is also, unusually, the principal neuron and projecting neuron of this microcircuit. Synaptic depression dominates most synapses in all microcircuits, but synaptic facilitation seems most rare in the spinal cord and most common in the neocortex. The use of synaptic depression is a powerful core mechanism for synchrony and oscillations [99], and the use of synaptic facilitation can further diversify the form of oscillations that are possible (Melamed, Silberberg, Markram & Tosdyks, unpublished).

While all these microcircuits can oscillate at different frequencies (see Grillner et al., this issue) using different microcircuit designs, the burning question is whether these different designs are used to perform fundamentally different computations.

On the one extreme, a slight "touch" can trigger a spinal cord microcircuit to produce a precise and repeatable rhythmic cycle which can be described as falling into a low energy valley of an activity landscape (attractor states), where the circuit may wander indefinitely until retrieved by another touch, just to be thrown into a different attractor valley. Here stereotypical microcircuits are required to perform a very specific and precisely repeatable task. This form of computing can be called "low entropy computing". Such microcircuits may be important to allow certain brain functions to run autonomously, such as breathing and walking.

On the other extreme, the real-world presents to the neocortex a multidimensional sensorial movie which constantly pulls the activity state out of the attractive valleys and their autonomous unconsciousness, to process the next unexpected moment. Neocortical microcircuits must therefore spend much more time out of attractor valleys in cross-country trajectories while performing meaningful computations on the world. This form of computing can be called "high entropy or liquid computing".

In order to efficiently compute in real-time and in a real-world there is an increasing evolutionary demand for predictive microcircuits that hold and simulate internal models of the world. These internal models and their functionality are probably embedded within the precise structural and functional design of the microcircuit through inheritance and learning. When activated, the activity state of these microcircuits also falls into valleys of certainty and predictability and therefore also displays a range of oscillatory or other predictable behaviours (see Grillner et al., this issue). This attractor-like behaviour has tempted many to believe that the neocortex is a giant collection of CPGs [100] and that the neocortex merely represents an "encephalization of motor rhythms" [101].

The problem however, is to process continuously changing inputs in real-time, to learn new associations in real-time, and to generate novel responses in real-time using information collected at any combination of moments back in the past. "Encephalization" therefore must solve the high entropy problem. This difficult challenge can be solved by microcircuits acting as deterministic high dimensional dynamical systems [102].

Arguably, cognition arises from the ability to simulate the world in order to anticipate events as far in the future as possible. An ideal neural predictor could be without any need for continual sensory input since it would be able to build and simulate the world indefinitely into the future. In reality however, constant updates are required to correct the internal model and it's functionality by adding new parameters for associations and prevent hallucinatory trajectories. For cognitive microcircuits therefore, while the predicted world may emerge from the microcircuit design, the moment-to-moment information about the world, probably lies in the *displacement* (surprised) from these predictions (i.e. displacement from the attractor state/displacement from the functional maps commonly seen). The neocortex may have "discovered" how to make sense of such surprised moment or high entropy displacements by using precise mapping of neurons, layers, columns and regions onto each other and using constant learning to understand a continuously changing and perhaps never repeating activity state.

While the thalamus may help the neocortex solve this task by organizing and topographically mapping the sensory world onto specialized regions of the neocortex, the hippocampus could help by building a map of associations between all parameters of the internal model and it's functionality – a cognitive map [103]. The lack of strong recurrent excitation in the hippocampus and the presence of relay circuits are striking features, suggesting that the hippocampus builds such a map by sequential mapping onto dentate, CA3 and then CA1, with inhibition controlling which parameters to associate. Such a cognitive map may be essential to help the neocortex solve the high entropy problem since perhaps the great greatest challenge for the neocortex is to learning new associations and prior sorting and organization of these associations may be crucial.

In its simplest form, the cerebellar cortex is a feedforward, adaptive circuit driven by both central and peripheral input (see [104] for a review of models and theories). The discrepancy between the numbers of input and output fibers suggests that the cerebellum signals rare events, or that it is involved in the computation of transformations to a lower-dimensionality space. Such computations are typically related to broad classification task. A continuous comparison of the actual peripheral input with that predicted to occur following a central motor command (the internal model) may enable fast error correction. Alternatively, repeated presentation of the central and peripheral inputs may teach the cerebellum to generate motor output in an

autonomous manner, decoupled from central guidance. Simulations of computer models are needed to elucidate how the intrinsic dynamics of the cerebellar circuit, which is an inhibitory network, may contribute to these tasks.

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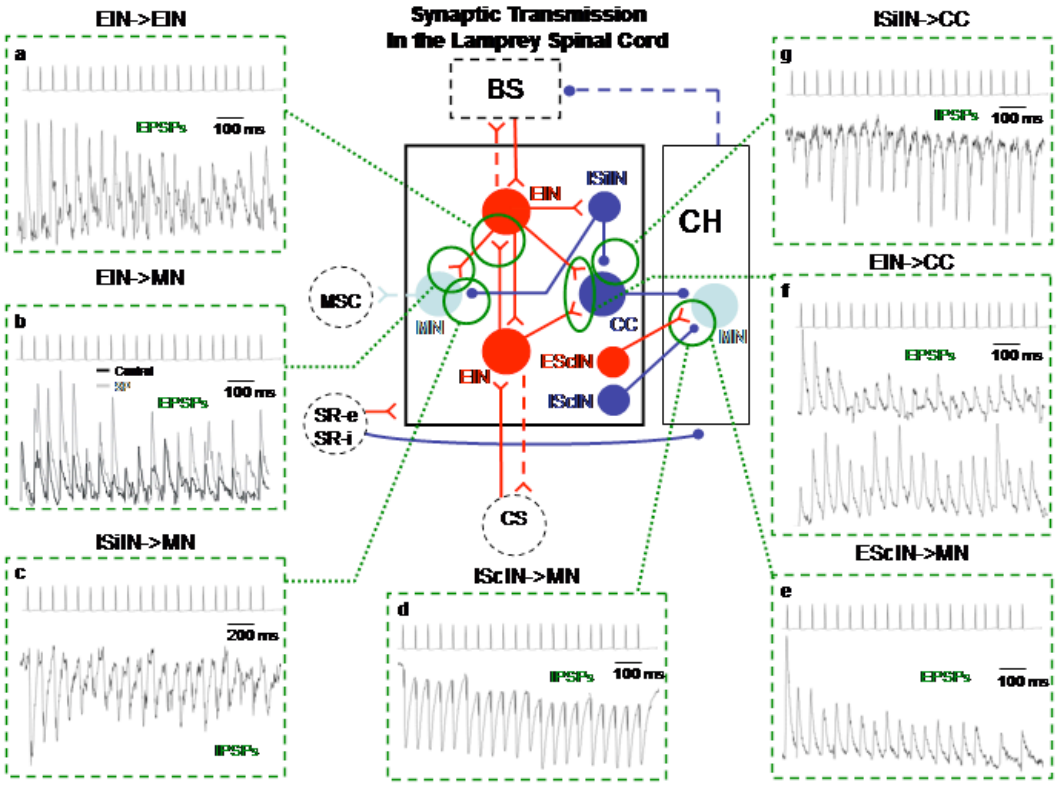

Figure 1

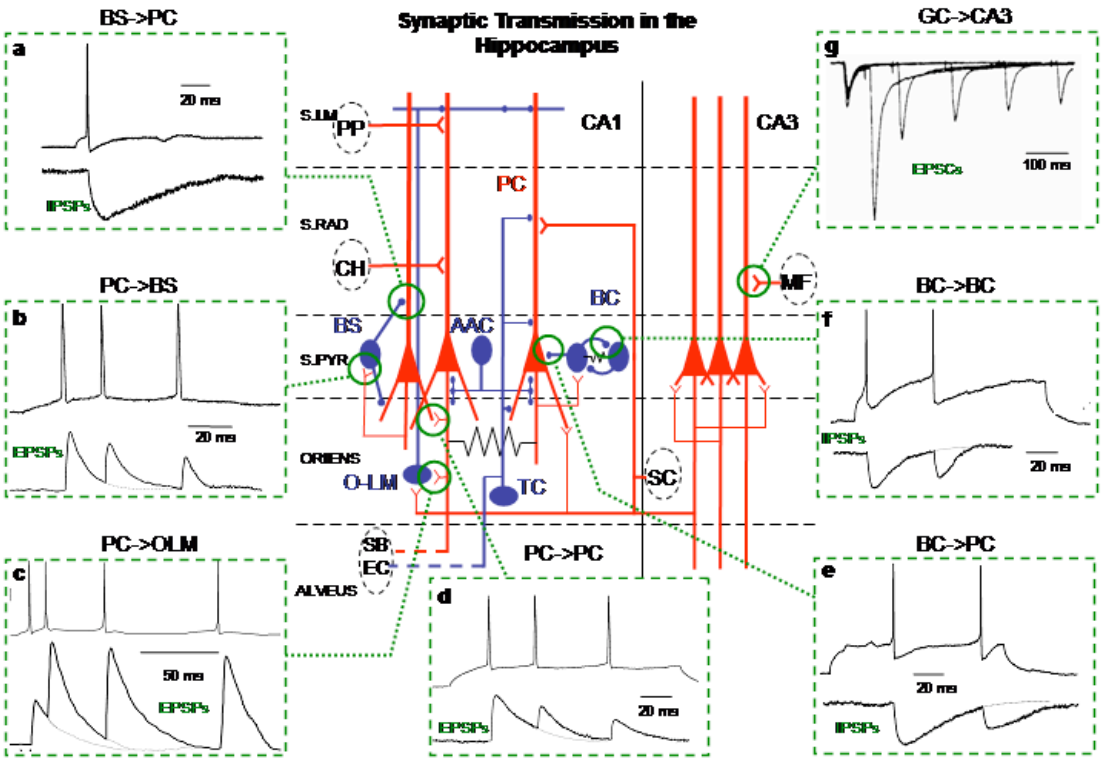

Figure 2

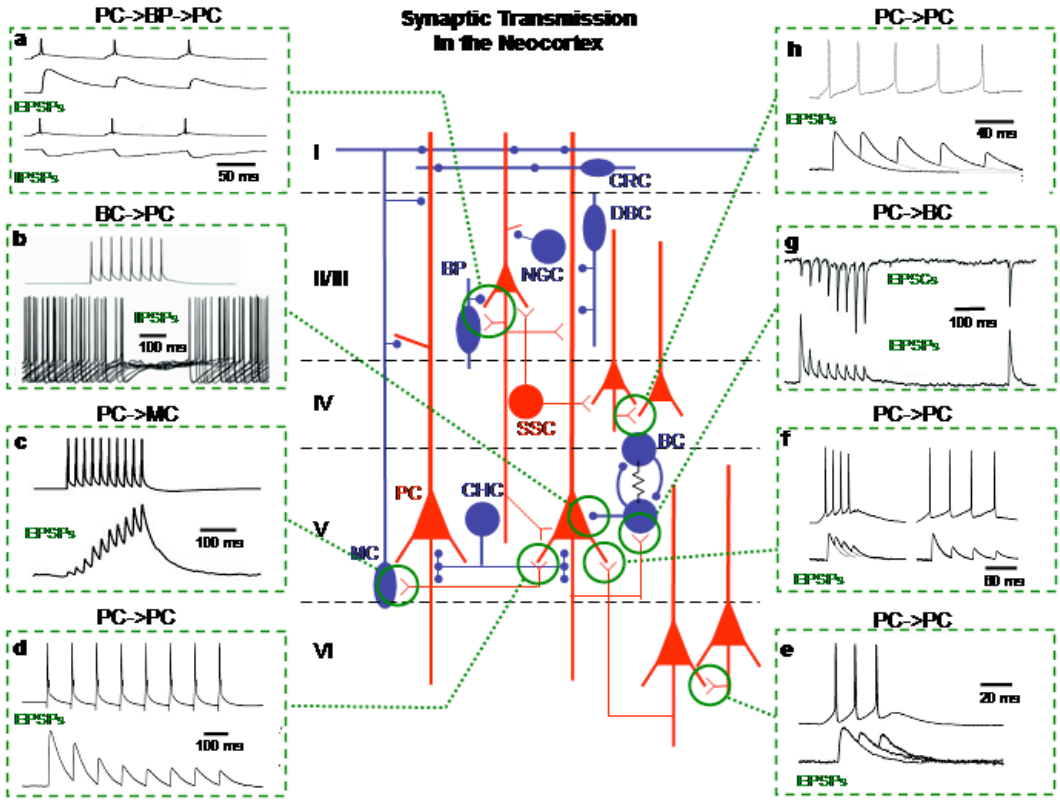

Figure 3

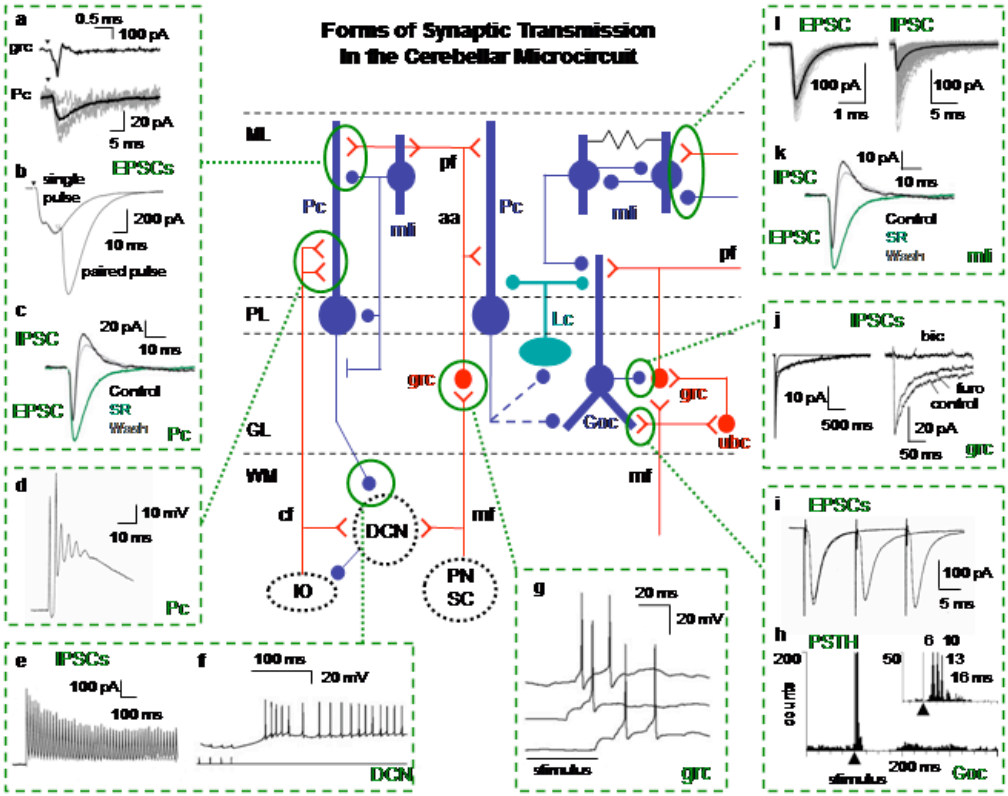

Figure 4

Figure Legends

Figure 1. Synaptic transmission in the spinal cord: The scheme in the centre represents the main neuron types and synaptic connections in the lamprey spinal cord. Excitatory glutamatergic neurons in red, and inhibitory glycinergic neurons in blue. Abbreviations: EIN: excitatory interneuron, CC: inhibitory commissural neuron, ScIN: small commissural interneuron (IScIN: inhibitory, EScIN: excitatory), ISiIN: inhibitory small ipsilateral interneuron, MN: motor neuron, BS: brainstem, CS: caudal segments, CH: contralateral hemi-cord, MSC: muscles, SR-e: excitatory sensory, SR-i: inhibitory sensory. The different types of connections are depicted in the inserts, with a schematic of the presynaptic train on top and the postsynaptic responses at the bottom: **a**. depressing excitatory connection between EINs. **b**. facilitating effect of substance P (grey trace, control in black) on an excitatory connection between EIN and ipsilateral MN. **c.** depressing inhibitory connection between ISiIN and MN. **d**. facilitating synapse between IScIN and the contralateral MN **e**. depressing synapse between EScIN and the contralateral MN. **f**. two types of synaptic dynamics (depression and facilitation) in excitatory connections between EINs and CC inhibitory neurons. **g**. facilitating inhibition between ISiIN and CC. All figures reprinted from [7,8].

Figure 2. Synaptic transmission in the hippocampus: The scheme represents the main neuron types and synaptic connections in hippocampal area CA1. Excitatory glutamatergic neurons in red, and inhibitory GABAergic neurons in blue. Abbreviations: AAC: axo-axonic cell, BC: basket cell, PC: pyramidal cell, BS: bistratified cell, OLM: oriens-lacunosum moleculare cell, TC: trilaminar cell, SC: schaffer collateral, MF: mossy fiber, PP: perforant pathway, SB: subiculum, EC: entorhinal cortex, CH: contralateral hemisphere, GC: granular cell. The different types of connections are depicted in the inserts, : **a**. inhibitory connection between BS to PC. **b**. depressing excitatory connection between PC and BS. **c**. facilitating excitatory connection between PC and OLM cell. **d**. depressing excitatory connection between PCs in CA1. **e**. depressing inhibitory connection between BC and PC. **f**. depressing inhibitory connection between BCs. **g.** facilitating excitatory connection between GC and CA3 PCs. Figure **g.** reprinted from [28]. Other figures reprinted from [31,42,105], including unpublished data by Audrey Mercer and Alex Thomson.

Figure 3. Synaptic transmission in the neocortex: The scheme represents the main neuron types and synaptic connections in the neocortex. Excitatory glutamatergic neurons in red, and inhibitory GABAergic neurons in blue. Abbreviations: CHC: chandelier cell, BC: basket cell, PC: pyramidal cell, BP: bipolar cell, MC: Martinotti cell, BTC: bitufted cell, DBC: double-bouquet cell, NGC: neurogliaform cell, SSC: spiny-stellate cell, CRC: Cajal-Retzius cell. The electrophysiological properties of the different types of synapses are depicted in the inserts. The presynaptic action-potential train is depicted above the postsynaptic response (except in **fig. 3g**, where only postsynaptic traces are shown). **a**. reciprocal depressing connection between PC and BP (reprint from [75]). **b**. depressing inhibitory connection between BC and PC (reprint from [76]). **c**. facilitating excitatory connection between PC and MC (reprint from [74]). **d**. depressing excitatory connection between L5 PCs (reprint from [106]). **e**. depressing excitatory connection between L6 PCs (modified from [62]). **f**. depressing excitatory connection between L6 PC and L5 PC (modified from [62]) .**g**. depressing and facilitating excitatory connections between PC and NBC (reprint from [76]). **h**. depressing excitatory connection between L4 PCs (Peter Bannister & Alex Thomson, unpublished).

Figure 4. Synaptic transmission in the cerebellum: Frontal view through a cerebellar folium showing the three-layered cortex whose principal neuron, the Purkinje cell (Pc), inhibits the neurons of the deep nuclei (DCN). The layer of Pc somata (PL) separates the granular layer (GL), through which the afferent climbing fibers (cf) and mossy fibers (mf) enter, from the molecular layer (ML), which is primarily occupied by the dendrites of Pcs and parallel fibers (pf). Pfs are the horizontal axon branches of granule cells (grc). Note that, apart from the cfs and mfs, only grcs and unipolar brush cells (ubc) are glutamatergic *(red)*; all other cortical neurons are GABAergic *(blue)*, the Lugaro cell (Lc) is mixed GABAergic-glycinergic (*magenta*). The cf excites the Pc monosynaptically, whereas mfs excite the Pc disynaptically over intermediate grcs. Grc-Pc synapses are found on the ascending grc axon (aa) and on pfs. Adult Pcs do not express NMDARs, hence their excitation by grcs is mediated through AMPAR synapses (**a**, dual recording of a unitary grc-Pc connection with $GABA_A$Rs blocked, illustrating stimulation of a grc in loose cell-attached mode and the evoked Pc EPSC [87]), which exhibit modest paired-pulse facilitation (**b**, EPSCs evoked by single-pulse

and paired-pulse pf stimulation [107]). The pf-evoked EPSC is followed by an IPSC mediated through $GABA_AR$ synapses from ML interneurons (mli) (**c**, monosynaptic EPSC and disynaptic IPSC evoked by pf stimulation; SR, $GABA_AR$ antagonist [89]). Note that interneurons exert inhibition on Pcs GABAergically, through synapses on the Pc dendrite and soma, but presumably also electrically through a unique, axoaxonal juxtaposition. The second afferent, the cf originating from the inferior olive (IO), evokes in its single, target Pc a dendritic Ca^{2+} spike with few somatic Na^+ spikes superimposed, called a complex spike (**d**, [108]). Pcs have a high spontaneous actvity (30-50 Hz), which evokes in neurons of the DCN IPSCs with moderate short-term plasticity (**e**, IPSCs in a DCN neuron evoked by 50 Hz stimulation of the corticonuclear tract [90]). The DCN neuron typically fires a rebound burst when relieved of inhibition (**f**, discharge in a DCN neuron following 56 Hz stimulation of corticonuclear tract [91]). The right half of the figure depicts many recurrent connections, with an emphasis on the control exerted by Golgi cells (Goc) on the mf-grc connection. Mfs, originating mainly from precerebellar, brainstem nuclei (PN) and the spinal chord (SC), form numerous glomeruli in the GL, each exciting tens to hundreds of grcs. Each grc has four mf afferents, making mixed AMPAR-NMDAR synapses, but fires upon summation of two EPSPs (**g**, grc responses evoked by facial stimulation, recorded through patch-clamp *in vivo* [82]). The Goc, in addition to its pf input, presumbaly also receives monosynaptic mf excitation, as indicated by its short-latency, robust responses *in vivo* (**h**, peristimulus time histogram of Goc response evoked by 200 trials of punctate facial stimulation; bin width 2 ms, 0.5 ms in inset [86]) and *in vitro* (EPSCs evoked by paired-pulse stimulation of white matter (WM); average traces of 10 ms and 20 ms pulse interval superimposed (S. Dieudonné, PhD thesis, Université Pierre et Marie Curie, Paris VI, 1998)). A Goc spike evokes a phasic IPSC in grcs, having a slow spill-over component (**j**, left), which is completely abolished by bicuculline (*bic*) and partly by furosemide (*furo*) (**j**, right) indicating mediation by $GABA_A$ receptors containing α_6 subunits [84]. In the ML, interneurons (mli) are reciprocally connected through electrical and $GABA_AR$ synapses. Mlis, like Pcs, receive monosynaptic excitation and disynaptic inhibition from pfs (**k**, compare with **c**), and are sensitive to single quanta of released transmitter (**l**, miniature EPSCs and IPSCs in the presence of the NMDAR antagonist CPP [88]). All panels show data from rat and were reproduced, with permission, from [87] (**a**), [107] (**b**), [89] (**c** and **k**), [108] (**d**), [90] (**e**), [91] (**f**), [82] (**g**), [86] (**h**), [84] (**j**) and [88] (**l**).