Cogn Neurodyn (2015) 9:463–477
DOI 10.1007/s11571-015-9337-1

REVIEW PAPER

Information processing in the CNS: a supramolecular chemistry?

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Received: 23 June 2014 / Revised: 2 February 2015 / Accepted: 3 March 2015 / Published online: 10 March 2015

Abstract How does central nervous system process information? Current theories are based on two tenets: (a) information is transmitted by action potentials, the language by which neurons communicate with each other—and (b) homogeneous neuronal assemblies of cortical circuits operate on these neuronal messages where the operations are characterized by the intrinsic connectivity among neuronal populations. In this view, the size and time course of any spike is stereotypic and the information is restricted to the temporal sequence of the spikes; namely, the "neural code". However, an increasing amount of novel data point towards an alternative hypothesis: (a) the role of neural code in information processing is overemphasized. Instead of simply passing messages, action potentials play a role in dynamic coordination at multiple spatial and temporal scales, establishing network interactions across several levels of a hierarchical modular architecture, modulating and regulating the propagation of neuronal messages. (b) Information is processed at all levels of neuronal infrastructure from macromolecules to population dynamics. For example, intra-neuronal (changes in protein conformation, concentration and synthesis) and extra-neuronal factors (extracellular proteolysis, substrate patterning, myelin plasticity, microbes, metabolic status) can have a profound effect on neuronal computations. This means molecular message passing may have cognitive connotations. This essay introduces the concept of "supramolecular chemistry", involving the storage of information at the molecular level and its retrieval, transfer and processing at the supramolecular level, through transitory non-covalent molecular processes that are self-organized, self-assembled and dynamic. Finally, we note that the cortex comprises extremely heterogeneous cells, with distinct regional variations, macromolecular assembly, receptor repertoire and intrinsic microcircuitry. This suggests that every neuron (or group of neurons) embodies different molecular information that hands an operational effect on neuronal computation.

Keywords Information · Processing · Action potential · Neural code · Supramolecular · Macromolecule · Embodiment

Introduction

How does central nervous system (CNS) process information[1]? This crucial question forms part of the more general effort aimed at establishing causal relations between specific aspects of neuronal activity and system-level consequences (Gollisch 2009).

All the current paradigms in neuroscience, such as the computational models (Rumelhart et al. 1986; Qu et al. 2014; Kim and Lim 2013), the Bayesian brain and free-energy hypothesis (Friston 2010), the connectome (Sporns 2013), the fractal dimension analysis (Ibáñez-Molina and Iglesias-Parro 2014; Mattei 2014), the early multisensory

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[1] It is important to define what we mean by "information" and "information processing" in CNS. By "information" we will assume an ordered sequence of symbols from an input and an output alphabet. With the term "information processing" we will assume a function that maps any input sequence sample from an input alphabet into an output sequence from an output alphabet (Wicker and Kim 2003).

integration (Klemen and Chambers 2012), are based on two tenets:

(1) Information is contained in the electric currents generated by neurons. Neurons process information, which is passed by action potentials—the language by which neurons communicate with each other (Gollisch 2009). To give an example, all sensory data are initially encoded as voltage changes in sensory receptors; these noisy and ambiguous signals are processed by the peripheral nervous system and brain to produce percepts and qualia, experienced as sharp, certain and unambiguous (Brown H, Friston K: Resolving Uncertainty in Perception, Research topics 2013).
(2) The cells of neural circuits are not characterized computationally by their morphology or specific protein content, rather by the intrinsic and extrinsic connectivity they exhibit. In this view, cortex is generally regarded as homogenous, all areas being composed of a basic repeated circuit (Elston and Rockland 2002), sometimes referred to as a canonical microcircuit. Functional specificity is determined by the source of inputs and, implicitly, the axonal connectivity among neurons (Xiumin 2014). It follows that the information transmitted by the neuron must be contained in the temporal sequence of the spikes, the "spike train". The relationship between stimulus, spike trains and transmitted information forms the "neural code", the crucial tool by which neurons recognize, represent, store and transmit information (Gollisch 2009). The term "code" thus means the representation of the facts about the stimulus in terms of neuronal spiking activity.

In summary, there is a broad consensus based on the concepts of action potentials, neural code and canonical microcircuits that emphasise a singular level of message-passing in the brain; namely, those messages mediated by action potentials. Current theories consider self-evident the foremost role of action potentials in communication and highlight their function in establishing distributed neuronal interactions across several levels (including brain regions, functional circuits and large-scale networks), usually within a hierarchical or modular architecture.

However, in the last decade, neuroscience has witnessed major advances at the molecular and extra-neuronal level: multiple lines of evidence now shed new light on information processing in CNS. The aim of this (theoretical) paper—based on recent innovations—is therefore to point towards an alternative perspective. This paper comprises four sections. The first section suggests that the role of action potential/neural code in information processing is less prominent than thought. "When it comes to the brain, wiring isn't everything. Although neurobiologists often talk in electrical metaphors, the reality is that the brain is not nearly as simple as a series of wires and circuits" (Newswire 2014). We will show that action potentials—rather than just processing information—may mediate other functions in the CNS. Section two links information processing to mechanisms other than action potential/neural code, emphasizing the role of biologically active molecules and macromolecules. This section introduces a scenario based on "supramolecular chemistry". Section three considers other (potentially underrated) mediators of information processing in CNS from a more holistic perspective, emphasising the circular causality among different spatial and temporal scales: in particular, we will focus on extra-neuronal factors and the potentially important role of peripheral receptors. The final section shows how, contrary to the standard model, neuronal populations are heterogeneous and every cell (or group of cells) embodies specific and unique molecular information.

A different role for the action potential?

How does the neural code work? What do spike patterns mean? This is a topic of intense debate within the neuroscience community. A range of different theories has been offered over the years: the paradigms of the rate or temporal codes, latency, relational, synchrony codes, variations or mixtures of them, and so on (Gollisch 2009). We hypothesize that action potentials play a role in local–global communication, modulating and regulating the processing of information (that is mediated by local processes entailed by the infrastructure of single neurons and microcircuits at multiple scales of organisation).

The evidence points towards cortical oscillations, cross-frequency phase coupling and representation of multiple time scales as tools for mediating interactions among functional cell assemblies in distributed brain circuits (Buzsáki and Watson 2012). Synchronized neuronal activity does not seem to contain a specific code, rather to operate as a generic mechanism capable of binding together neural activities of spatially separated cortical areas and dynamically shaping task-relevant neural ensembles out of larger, overlapping circuits (Buschman et al. 2012).

The main function of electric pulses appears to be to regulate information processing. The brain uses synchronized activity to establish or select network connections and to organize complex information, such as sensory inputs. Recent studies are in accordance with in vivo observations related to the coordination of neuronal

processing and point towards the hypothesis that timing is crucial. To give some examples:

- Recent works underline the special role of neuronal synchrony in pattern recognition. A framework has been proposed in which inhibitory alpha oscillations limit and prioritize neuronal processing (Jensen et al. 2014). During spatially distributed representations in early visual regions, inhibition prevents neuronal firing. As the inhibition ramps down within a cycle, a set of neuronal representations will activate sequentially according to their respective excitability. Both top-down and bottom-up drives determine excitability; in particular, spatial attention constitutes a major top-down influence. On a shorter time scale, fast recurrent inhibition segments representations in slots 10–30 ms apart, generating gamma-band activity at the population level (Jensen et al. 2014). Other data suggest that, in the frontal cortex, beta-frequency synchrony selects the relevant rule ensemble, while alpha-frequency synchrony deselects a stronger, but currently irrelevant, ensemble (Buschman et al. 2012). Furthermore, 20–40-Hz oscillations have been identified as a mechanism for synchronizing evolving representations in dispersed neural circuits, during encoding and retrieval of olfactory-spatial associative memory (Igarashi et al. 2014).
- The study of temporal windows in visual perception (and attention) shows how oscillatory dynamics play a role in carving successive visual inputs into separate perceptions, with higher beta power associated with incorrect perception of the target and evoked alpha phase reset associated with correct target perception (Wutz et al. 2014).
- Rapidly changing brain states during learning may be encoded by the synchronization of oscillations across different brain regions. Waves originating from prefrontal cortex and striatum are involved in learning associations to form new communication circuits when monkeys learn to categorize different patterns of dots (Antzoulatos and Miller 2014). The role of waves, in this case, is to synchronize and enable faster learning.
- The sensitivity of neuronal activity to the timing of synaptic inputs suggests that synchrony determines the propagation of information and, in turn, regulation of synchrony is a critical element. The developing brain in Xenopus tadpolere wires and fine-tunes its connections differently depending on the relative timing of sensory stimuli (Munz et al. 2014). Asynchronous firing not only causes brain cells to lose their ability to make other cells fire, but induces a 60 % increase in axonal branching. The stabilization of retinal nerve cell branches caused by synchronous firing involves signalling downstream of the synaptic activation of the *N*-methyl-D-aspartate receptor. In contrast, the enhanced exploratory growth that occurs with asynchronous activity does not appear to require the activation of this receptor (Munz et al. 2014).
- The time scale of practice affects patterns of brain activity associated with motor skill acquisition. Activity in the striatum is consistently more rostral in the intermediate time scale and more caudal over longer time scales. These data support neurophysiological models that posit that systems are active, but at different time points, during motor learning (Lohse et al. 2014).

Gamma-band activity and the synchronization of neural activity in the gamma-frequency range, observed ubiquitously in different cortical and subcortical structures, have been associated with different cognitive functions and reflect neuronal network coordination involved in attention, learning and memory (Kucewicz et al. 2014; Brunet et al. 2014). However, it is still unknown whether gamma-band synchronization subserves a single universal function and reflects a global recognition signal, or a diversity of functions across the full spectrum of cognitive processes. This question has been addressed by Bosman et al. (2014), who stresses that gamma oscillations, associated with interplay between inhibition and excitation, originate from basic functional motifs that confer advantages for low-level system processing and multiple cognitive functions throughout evolution. The multifunctionality of gamma-band activity is confirmed by its role in neural systems for perception, selective attention, memory, motivation and behavioural control. Thus, gamma-band oscillations seem to support multiple cognitive processes, rather than a single one.

In summary, even under the standard model of neuronal message passing (through temporally coordinated action potentials), a picture emerges that speaks directly to circular causality among different temporal scales. Circular causality of this sort is a characteristic of self-organised dynamical systems (most formally characterised in synergetics). It suggests that any dynamical system can exhibit modes of behaviour which separate into slow and fast timescales. Typically, the fast modes are local and dissipate quickly; while slow modes are more global and decay more slowly (the amplitudes of these slow modes are known as order parameters). Crucially, the slow modes are simply the superposition or average of fast modes, while—at the same time—the slow modes enslave and contextualise the fast modes. This is the essence of circular causality between different timescales. In the context of the oscillatory brain dynamics considered in this section, one could regard distributed and synchronised (global) modes as the slow modes that contextualise standard (action potential) message passing to mediate the sorts of phenomena we

associate with attention and the gating (or selection) of particular patterns of connectivity (or interactions). If this view is correct, then simply equating neuronal codes with firing rates of action potentials is an incomplete description of neuronal dynamics; because it fails to accommodate the dynamic coordination implicit in self-organised activity—and evidenced by the neuromodulatory effects of distributed synchronous activity in the brain. In the next section, we extend this argument to cover not just different temporal scales, but also spatial scales of neuronal systems.

The function of biologically active molecules and/or macromolecules in information processing

Traditionally, in neuroscience the emphasis is on evaluating cognition from a computational point of view. However, studies in biologically inspired robotics and embodied intelligence provide strong evidence that cognition cannot be analyzed and understood by looking at computational processes as a single level, but that physical system–environment interaction needs to be taken into account. According to some authors, we need to build our understanding of cognition from the bottom up; that is, all the way from how our body is physically constructed (Pfeifer et al. 2014). A connection between cognition, body morphology and soft material properties has been pursued, showing how physics-based approaches have led to new insights into biological systems at all scales of space and time, at all levels of complexity, including information processing in CNS (Foffi et al. 2013).

The recent idea of "supramolecular chemistry" (the so called "chemistry beyond molecule"), has paved the way towards appreciating chemistry as an information science, the science of informed matter (Lehn 2007). Complex chemical entities can be reversibly constructed from molecular components bound together by labile non-covalent interactions. The novel concept of molecular information involves the storage of information at the molecular level and its retrieval, transfer and processing at the supramolecular level, via transitory molecular processes that are self-organized, self-assembled and dynamic (Lehn 2007). Sequential, hierarchical self-organization on increasing scale and constitutional dynamics in non-equilibrium systems can lead to the emergence of novel features/properties at each level, organization in space as well as in time and passage beyond reversibility. This perspective is particularly relevant for the brain that is probably the best example of an open system which maintains non-equilibrium steady-state (i.e., homoeostasis or allostasis) in the face of environmental fluctuations.

The complexity of the biological milieu calls for more refined descriptions when entering the domain of biological sciences. To what extent does the strong spatial inhomogeneity (clustering, cellular compartmentalization, and so on), diffusion, excluded volume, electrostatic and hydrodynamic interactions have to be taken into account? The experimental evidence is still controversial, but recent results suggest that interactions affect the kinetics of self-assembly reactions. Crowding-induced changes in the structure and dynamics of macromolecules describe a scenario of systems capable of generating well-defined functional supramolecular architectures by self-assembling from their components, thus behaving as programmed chemical systems. For example, it has been demonstrated that small variations in the genetic code—thought to be inconsequential (involving genes with diverse functions in endocytosis, oxidative stress response, RAS-cAMP signalling and transcriptional regulation of multicellular growth)—that have not previously been shown to exhibit functional relationships—and do not individually appear to have much effect—collectively lead to significant changes in an organism (Taylor and Ehrenreich 2014).

Incorporating this perspective appears to be crucial for understanding the dynamics of biological systems in vivo and suggests that this approach is also valid in neurobiology (Foffi et al. 2013). Indeed, the current day concepts about synaptic transmission, intraneuronal signaling and interactions between neuronal genome, proteome and metabolome are in line with the basic principles exposed by Lehn: hence, the ideas about supramolecular chemistry are implicitly incorporated in the recent neurobiological research. At present there are clues that speak to neuronal processing that rests on macromolecules, rather than just electric pulses. Scientists are starting to address the important problem of whether cellular signals can also travel long distances in a crowded environment (c.f., action potentials). There follows a list of recent papers (that pertain to the molecular neurobiology of cognitive functions), which demonstrates that gene expression within neuronal populations and changes in molecular/macromolecular conformation, number or synthesis, can mediate different neural functions:

- A recent "experimentum crucis" explains why different sets of the same protein variations occur in one neuron and how this contributes to the complex wiring. In the Drosophila, the neuron can create many isoforms from the same Dscam1 protein on its cell surface (He et al. 2014). The specific set of isoforms of Dscam1 receptor determines the neuron's unique molecular identity and plays an important role in establishing accurate connections and for neuronal self-recognition and self-avoidance. Different sets of Dscam1 isoforms occur also inside one axon and lead to dominant dosage-sensitive inhibition of branching. Thus, cell-

intrinsic use of surface receptor diversity is of general importance in regulating axonal branching during brain wiring (He et al. 2014).

- Neurexin isoforms are generated via alternative splicing at multiple independent sites and have power over cognitive functions (Treutleina et al. 2014). For instance, Neurexin 1a and 2 and CNTNAP2, all members of the neurexin superfamily of transmembrane molecules, have been implicated in neuropsychiatric disorders (Karayannis et al. 2014).
- Researchers reported changes in 352 proteins in rat brain 15 min after phencyclidine injections. The transitory modifications started a chain reaction of changes in the molecular network around the proteins, such as changes in cell metabolism and calcium balance, transport of substances into and out of cells and in the structure of the cytoskeleton, causing the rats to change their behaviour (Palmowski et al. 2014).
- An astonishing three-dimensional model of an "average" synapse has been generated, displaying 300,000 proteins in atomic detail. Copy numbers varied over more than three orders of magnitude between steps, from about 150 copies for the endosomal fusion proteins to more than 20,000 for the exocytotic proteins (Wilhelm et al. 2014).
- Researchers have identified key genes linked to people showing a higher tolerance for pain than others. The DRD1 gene variant was 33 % more prevalent in the low pain than in the high pain group. Among people with a moderate pain perception, the COMT and OPRK variants were 25 and 19 % more often found than in those with a high pain perception. The DRD2 variant was 25 % more common among those with a low pain threshold compared to people with a moderate threshold (Onojjighofia 2014).
- FoxP mutants take longer than wild-type flies to make decisions in odour discriminations of similar or reduced accuracy, especially in difficult, low-contrast tasks. RNA interference with FoxP expression in αβ core Kenyon cells, or the over expression of a potassium conductance channel in these neurons, is recapitulated the FoxP mutant phenotype. A mushroom body subdomain, whose development or function requires the transcription factor FoxP, supports the progression of a decision toward commitment (DasGupta et al. 2014).
- Mn2+ accumulates intracellularly on injection into the motor neurons in the buccal network of living Aplysia, its concentration increases when the animals are presented with a sensory stimulus (Radecki et al. 2014).
- Different types of neurons traffic microRNA to distinct membrane locations, affecting the functional response of neurons: Extracellular let-7b, a microRNA found in the CNS, affects neurons through its interaction with Toll-like receptor 7 (TLR7), but with divergent outcomes in different neurons. Indeed, let-7b stimulation of cortical and hippocampal neurons leads to neuronal apoptosis, whereas let-7b activation of TLR7 stimulated the cation channel transient receptor potential A1 (TRPA1) on the dorsal root ganglia sensory neurons and induced pain responses. The primary difference that influences these distinct responses is the localization of TLR7 to the endosome in the cortical and hippocampal neurons, or the plasma membrane in the sensory neurons (Winkler et al. 2014).

Different aspects of molecular signalling relevant to the formation of memories have been extensively studied. The most recent papers highlight the numerous molecular mechanisms that underlie memory processing:

- MAPK and PKA signalling cascades are spatiotemporally integrated in a single neuron, to support synaptic plasticity underlying memory formation (Ye et al. 2012).
- Prion-based mechanisms provide a durable molecular memory, involved in long-term memory formation (White-Grindley et al. 2014).
- Fatty Acid-binding Protein 5 (FABP5) enhances learning and memory functions in the brain hippocampus region, both by decreasing anandamide levels and by activating the Nuclear Receptor Peroxisome Proliferator-activated Receptor β/δ. FABP5 delivers endocannabinoids to cellular machinery that breaks them down and shuttles compounds to a transcription factor that increases the expression of cognition-associated genes (Yu et al. 2014).
- RGS7 plays a part in hippocampal synaptic plasticity. GABA shapes the activity of the output pyramidal neurons via RGS7, in cooperation with its binding partner R7BP. Deletion of RGS7 in mice dramatically sensitizes responses to GABAB receptor stimulation and markedly slows channel deactivation kinetics. As a result, mice lacking RGS7 exhibit deficits in learning and memory formation (Ostrovskaya et al. 2014).
- The retrosplenial cortex engages in the formation and storage of memory traces for spatial information: the spatial memory consolidation is enhanced by over expression of the transcription factor CREB with a viral vector (Czajkowski et al. 2014).
- The fruit fly Drosophila melanogaster has a dedicated mechanism for active forgetting: blocking the G-protein Rac leads to slower, and activating Rac to faster forgetting (Brea et al. 2014).
- The spatial positioning of proteins at specific areas around neurons predicts which memories are recorded (O'Donnell and Sejnowski 2014).

Finally, other types of neuronal infrastructures, apart from spikes, are used by neurons for information processing. These include the following examples:

- Neurons utilize secretory events, both to process information and to fine-tune the release of neuropeptides. For example, a localized intracellular store of calcium is needed to initiate the secretion of neuropeptides (McNally et al. 2014).
- Evaluating the spatial and temporal characteristics of vesicle transport has important implications for our understanding of cognitive pathways. In a neuronal culture system from Drosophila larval brains, scientists visualized the movement dynamics of several cargos/organelles along a 90 micron axonal neurite over time. All vesicles/organelles showed robust bi-directional motility at both day 1 and day 2. Reduction of motor proteins decreased the movement of vesicles/organelles, with increased numbers of neurite blocks and neuronal growth perturbation. Strikingly, all blockages were not fixed and permanent as previously thought, but some blocks were dynamic clusters of vesicles that resolved over time (Iacobucci et al. 2014).
- Mitochondria have a central role in neuronal physiology. Axonal mitochondria undergo spontaneous "contractions", accompanied by reversible redox changes. These contractions are amplified by neuronal activity and constitute respiratory chain-dependent episodes of depolarization coinciding with matrix alkalinization, followed by uncoupling (Breckwoldt et al. 2014). Furthermore, recent results indicate that adult hippocampal neurogenesis requires adaptation of the mitochondrial compartment. The development of new neurons from stem cells in the hippocampus of adult mice is paralleled by extensive changes to mitochondrial mass, distribution and shape. Genetic inhibition of the activity of the mitochondrial fission factor dynamin-related protein 1 (Drp1) inhibits neurogenesis under basal and exercise conditions. Conversely, enhanced Drp1 activity furthers exercise-induced acceleration of neuronal maturation (Steib et al. 2014).

In summary, based on recent data, we hypothesize that, although all neurons exhibit a common repertoire of macromolecules, each one embodies a specific, non-covalent and transitory supramolecular assembly. This explains why each neuron is apparently similar to others, but functionally different. An important question arises: if macromolecules play a part in neuronal information processing, why has this link not been emphasised by the current paradigms that focus on electric pulses? One answer is that there are still many unexplored aspects, because protein dynamics is more sensitive than structure to environmental factors such as crowding, solvent, temperature, pressure, confinement. While in vitro experiments remain the only way to investigate the intrinsic properties of molecules, this approach ignores the fact that—in their natural milieu—proteins are surrounded by other molecules of different chemical nature, and this crowded environment considerably modifies their behaviour (Foffi et al. 2013). At present, the complexity of functionally interacting structures is beyond our current knowledge: biological macromolecules live and operate in a structured and complex environment within the cell—and the interior of the cell is by no means a simply crowded medium (Foffi et al. 2013). Due to the absence of well defined technical contributions directed to sustain that the concept of neural code must be introduced in a largest framework, neuroscientists are just starting to investigate the overwhelming (and probably unexpected) complexity of this system. The recent drafts of the human proteome (proteins encoded by 17,294 genes were identified, accounting for 84 % of the annotated protein-coding genes) (Kim et al. 2014a, b, c; Chen et al. 2014) are promising tools to obtain a better comprehension of supramolecular chemistry and to complement available human genome and transcriptome data. An impressive array of new tools and technologies is going to expand on the network aspects of cellular neurobiology and molecular neuroanatomy (Pollock et al. 2014). As an example, recent papers focused on the mechanisms of the multifaceted molecular reorganization of the inhibitory synapse during postsynaptic plasticity, with special emphasis on the key role of protein dynamics to ensure prompt and reliable activity-dependent adjustments of synaptic strength (Petrini and Barberis 2014). Last but not the least, much insight will be gained from the novel big data efforts in neuroscience, consisting in collections of large, open, high-throughput sets (Choudhury et al. 2014).

Information processing: not just neurons!

Structures quite different from neurons may also play a role in information processing in CNS. As an example, the extracellular medium is crucial for neuronal activity; some important examples include: substrate patterning and stiffness influence neuronal development by regulating its dynamics. Biophysical cues, such as the mechanical properties of the extracellular matrix, are known to modify neuronal differentiation and maturation (Sur et al. 2013). As noted above, the spatial positioning of proteins at specific areas around neurons predicts which memories are recorded (O'Donnell and Sejnowski 2014). Finally, a novel pathway found in the amygdala links fear-associated extracellular proteolysis of EphB2 to anxiety (Attwood et al. 2011).

These examples suggest that the external milieu of neurons provides an embodiment that dictates their function. In this section, we pursue the notion of embodied neuronal computation by listing some key examples of a circular causality (reciprocal exchange) between neurons and the environment. To illustrate the diversity and ubiquity of this (generalised) embodiment, we will focus on the neuronal infrastructure (white matter) itself, the role of bacteria and pathogens, the role of physiology and finally, of peripheral receptors.

Embodiment in connectome

In a similar vein, myelin plasticity helps to explain how the brain adapts in response to different stimuli. For example: myelin coverage along axons is not uniform as previously supposed and changes in white matter distribution may constitute a form of neuronal plasticity. In mice, individual neurons have a distinct longitudinal distribution of myelin, including a new pattern where myelinated segments are interspersed with long, unmyelinated tracts (Yates 2014). Furthermore, it has been demonstrated that the profile of longitudinal distribution of myelin is an integral feature of neuronal identity and that variability in the thickness of the envelope is a structural feature affecting the conduction of neuronal signals (Tomassy et al. 2014). Indeed, neuronal activity causes an increase in the thickness of the myelin sheaths within the active neural circuit, by promoting adaptive oligodendrogenesis (Gibson et al. 2014). Furthermore, changes in white matter microstructure in the superior cerebellar peduncles and primary motor cortex contribute to motor expertise and individual differences in ability (Roberts et al. 2013). Finally, leptin receptors are expressed in hypothalamic astrocytes involved in feeding control and their conditional deletion leads to altered glial morphology and synaptic inputs. In mice with astrocyte-specific leptin receptor deficiency, leptin-regulated feeding was diminished, whereas feeding after fasting or ghrelin administration was elevated (Kim et al. 2014a, b, c).

Commensal and pathogenic embodiment

Intestinal bacteria are also involved in many functions within CNS. Recent findings show that commensal bacteria can activate neural pathways and CNS signalling systems (Foster and Neufeld 2013). Several mechanisms have been proposed:

- Gut microbes alter levels of neurotransmitter-related metabolites affecting gut-to-brain communication. For instance, certain bacteria produce homovanillate—the breakdown product of dopamine—and *N*,*N*-dimethylglycine, a building block for proteins and neurotransmitters (American Society for Microbiology's annual meeting in Boston, Mass., May 17 to 20, 2014).
- It is known that gut hormones, such as peptide YY and glucagon-like peptide-1, directly affect neurons within the hunger-regulating hypothalamus. However, other unexpected intestinal agents may also influence the hypothalamus. A link between fermentation in the colon and activity in the brain has been traced. Acetate, released following the fermentation of dietary fibre in the mouse gut, accumulates in the hypothalamus and affects appetite (Frost et al. 2014).
- Stress increases intestinal permeability, causing gut bacteria to move into the systemic circulation. It is thought that circulating bacteria, offering a major source of Lipopolysaccharide, activate toll-like receptor (TLR) signalling pathways in the brain and subsequently induce neuroinflammatory responses. This process has been investigated in a rat model, suggesting that increased stress causes TLR-4 up-regulation in frontal cortex (Gárate et al. 2014).
- Finally, pathogenic microorganisms may affect brain functioning. Astonishingly, bacterial pathogens produce pain by directly activating sensory neurons that modulate inflammation (Chiu et al. 2013). It has been discovered that Staphyloccocus aureus induces calcium flux and action potentials in nociceptor neurons, via bacterial N-formylated peptides and the pore-forming toxin α-haemolysin (aHL). N-formyl peptides activate nociceptors by binding to FRP1 and inducing calcium flux, while αHL forms pores in the nociceptive cell membrane, allowing cation exchange (Chiu et al. 2013).

These and other studies suggest that the relationships between the CNS and immune system are more extensive and intimate than previously appreciated. A complex regulation of gene expression in neural cells in response to peripheral inflammation has been discovered. Recent observations reveal the existence of a previously unrecognized mechanism, based on extracellular vesicles that transfer functional RNA directly from the hematopoietic system to brain neurons, in response to inflammation and peripheral infections (Ridder et al. 2014). Reporter gene expression in neurons is caused by intercellular transfer of functional Cre recombinase messenger RNA from immune cells into neurons, in the absence of cell fusion. Although Cre-mediated recombination events in the brain is highly restricted in the healthy animal, inflammatory injuries increase both the frequency of transfer and the range of the neuronal target populations, extending beyond Purkinje neurons (Ridder et al. 2014).

Recent findings shed new light on the epigenetic basis of gene expression and molecular adaptations in brain.

Specific epigenetic mechanisms are involved in the stress response (Stankiewicz et al. 2013). These mechanisms (DNA methylation, histone modifications and microRNA activity) not only stably determine cell phenotype, but are also responsible for dynamic molecular adaptations of the limbic–hypothalamic–pituitary–adrenal axis to chronic psychogenic stressors. Traumatic experiences in early life alter mouse microRNA expression and metabolic responses in the progeny, via a molecular process of non-genetic inheritance of behavioural symptoms (Gapp et al. 2014). We speculate that variations in neural proteins due to epigenetic factors could explain the differences in functions of neurons, despite their apparent uniformity.

Molecular chaperones prevent aggregation and misfolding of proteins in the cellular environment and are thus central to maintaining protein homeostasis. Mechanisms of binding enables chaperones to function as holdases and unfoldases, by exerting forces to retain proteins in the unfolded state and at the same time protect them from aggregation by shielding their exposed hydrophobic regions from the solvent (Saio et al. 2014). The multiple binding sites recognize and interact with a large number of substrates with unrelated primary sequences. The fast kinetics enables chaperones to interact with transiently exposed, aggregation-prone regions of unstable proteins in the cytosol: we hypothesize that it could be one of the general mechanisms for the supramolecular chemistry described in Sect. 'The function of biologically active molecules and/or macromolecules in information processing'.

Physiological embodiment

It is well-known that basic physiological inputs can influence cognitions and emotions. Because bodily signals are constantly relayed to the neocortex, neural responses to them are likely to shape ongoing information processing, which in turn engages autonomic reflexes to change physiological (interoceptive) inputs. For example:

- In recent years, there has been an overwhelming increase in research on how nutritional factors influence cognition and behaviour. Neurocognitive performance is influenced by nutritional factors, ranging from the dietary level (e.g., whole diet and meal composition) to effects of macronutrients (glucose and omega-3 fatty acids) and micronutrients (vitamins, iron) (Smith and Scholey 2014).
- Metabolite concentrations reflect the physiological states of tissues and cells and may influence CNS functions (Bozek et al. 2014). In most species, chronic energy imbalance impacts olfactory-driven behaviours in response to food (Badonnel et al. 2014) and a high-fat diet leads to long-lasting structural and functional changes in the olfactory system (Whalley 2014).
- Short-term interoceptive fluctuations enhance perceptual and evaluative processes related to the handling of fear and threat, countering the view that baroreceptor afferent signalling is always inhibitory to sensory perception. The processing of brief fear stimuli is selectively gated by their timing in relation to individual heartbeats and these interoceptive signals influence the detection of emotional stimuli at the threshold of conscious awareness, altering judgments of emotionality of fearful and neutral faces (Garfinkel et al. 2014).
- Beyond conscious vision, physiological inputs underlie behaviourally relevant differential activation in multifunctional cortical areas. In humans, neural events locked to heartbeats before stimulus onset predict the detection of a faint visual grating in the posterior right inferior parietal lobule and the ventral anterior cingulate cortex. Heartbeats therefore shape visual conscious experience, potentially by contributing to the neural representations of the organism that might underlie subjectivity and a sense of self (Park et al. 2014).

Receptor embodiment

An underrated actor plays a crucial role in information processing in the CNS; namely, the peripheral receptor. To date, scientists have identified only a few of the receptors present on different types of nerve cells. However, research is ongoing: for example, using a new method, a group identified more than 400 receptors active in the sole warm sensitive neurons (Eberwine and Bartfai 2011). About one-third of them were "orphan" receptors, meaning the chemicals they bind to are unknown. Furthermore, a screening identified 194 candidate olfactory receptor genes linked to 11 odorants in the nematode Caenorhabditis elegans (Taniguchi et al. 2014).

Previously unrecognized sensory abilities are ceaselessly reported in animals. With the identification of additional receptors, we are gaining deeper insight into the mechanisms through which they process information.

- A self-recognition peripheral mechanism between skin and suckers in octopus prevents their arms from interfering with each other, via chemical signals that inhibit the attachment reflex (Nesher et al. 2014).
- Bumblebees can detect and discriminate the variations in pattern and structure exhibited by floral electric fields (Clarke et al. 2013).
- Some birds perform remarkable feats of navigation, using their different compasses: a star, a sun and a magnetic compass. Scientists do not yet understand how the birds' magnetic compass works, but there is

evidence that they use the quantum phenomenon of electron spin to navigate (Engels et al. 2014).

- Nematodes have concentration-dependent odour-sensing mechanisms, segregated at the olfactory receptor and sensory neuron levels. These neurons responded to high diacetyl concentrations only, whereas another class of chemosensory neurons react to both low and high concentrations. Chemosensory neurons ectopically expressing SRI-14 responded to a high concentration of diacetyl, resulting in avoidance responses (Taniguchi et al. 2014).
- A chloroplast retrograde signal regulates nuclear alternative splicing in plants. Light/dark conditions affect splicing of a subset of Arabidopsis genes preferentially encoding proteins involved in RNA processing (Petrillo et al. 2014).
- The sea catfish Plotosus japonicas is able to detect tiny changes in the water's pH level, changes indicating that the surrounding seawater has become slightly more acidic. The catfish senses local pH-associated increases in $H(+)/CO_2$ equating to a decrease of ≤ 0.1 pH unit in ambient seawater. This ability allows the fish to sense the breathing of prey hidden in the seafloor (Caprio et al. 2014).

Also human senses are under close investigation. Amazing novel "qualities" of receptors have been recently discovered in Homo sapiens:

- Recent observations suggest that protons might act as neurotransmitters. Protons, in concert with classical electric mechanisms, act directly as a nonquantal chemical neurotransmitter at vestibular hair cell-calyx afferent synapses (Highstein et al. 2014). Another study demonstrate that, in amygdala, postsynaptic receptors are acid-sensing ion channels, Na+- and Ca_2+-permeable channels, activated by extracellular acidosis. This process facilitates synaptic plasticity, a critical requirement for amygdala-dependent learning and memory (Du et al. 2014).
- The critical role of light for cognitive brain responses has been recently underlined. There is evidence in favour of a cognitive role for melanopsin, which may confer a form of "photic memory" to human cognitive brain function, via its wavelength-dependent, light-driven dual states (Chellappa et al. 2014).
- Merkel cells are primary sites of tactile transduction, and not Aβ-afferent nerve endings as previously believed. Scientists identified the Piezo2 ion channel as the Merkel cell mechanical transducer. Piezo2 transduces tactile stimuli into Ca(2+)-action potentials in Merkel cells, which drive Aβ-afferent nerve endings to fire slowly adapting impulses (Ikeda et al. 2014).
- There is mounting evidence that touch has another dimension, providing not only its well-recognized discriminative input to the brain, but also an affective input. It has been proposed that a class of low-threshold mechanosensitive C fibres that innervate the hairy skin represents the neurobiological substrate for the affective and rewarding properties of touch. C-fibres could be therefore involved in affect and reward, not just in pain (McGlone et al. 2014).
- Human visual gender perception draws on subconscious chemosensory biological cues, an effect that has been hitherto unsuspected. Indeed, a recent study suggests the existence of human sex pheromones, with particular interest in two human steroids, androstadienone and estratetraenol, which communicate opposite gender information in a sex-specific manner (Zhou et al. 2014).
- Unexpectedly, glucocorticoid hormone receptors have been found in the tongue. The highest concentrations were found in Tas1r3 taste cells, which are sensitive to sweet and umami taste (Parker et al. 2014). It suggests that hormones play a role in the detection of specific sensory qualities.
- The presence of carbohydrate in the human mouth has been associated with the facilitation of motor output. Oral receptors for carbohydrates have been identified as a potential mode of afferent transduction for this novel form of nutrient signalling, distinct from taste. Oral carbohydrate signalling increases activation within the primary sensorimotor cortex during physical activity and enhances activation of neural networks involved in sensory perception (Turner et al. 2014).

Receptors set in motion not only action potentials, but also a cascade of biochemical events correlated with information processing:

- Three single-point mutations in a single protein have been identified that can invert temperature-sensitivity, turning a cold-sensitive TRPA1 ion channels receptor for thermal pain into one that senses heat. The single-point mutation produced a profound change in the temperature sensitivity of the protein, but it did not affect the chemical sensitivity (Jabba et al. 2014).
- Mutations in the human gene encoding the Nav1.7 sodium channel can lead to either the inability to sense pain, or pain hypersensitivity. An antibody that blocks the NaV1.7 voltage-gated sodium channel in the neuronal cell membrane and suppresses pain in mice has been found to also simultaneously suppress itching in mice, even though pain and itch sensations usually follow different paths (Lee et al. 2014).

- During odour learning, molecular regulation of olfactory receptor expression contributes to plasticity in the olfactory system (Claudianos et al. 2014).
- Spike-based approaches to feature selectivity in sensory pathways focus on the most active neurons. However, a subthreshold method has been able to identify feature selectivity in the rodent vibrissal system, regardless of spiking activity (Shephard and Stanley 2014).
- Netrin-1, an axon-guiding molecule, affects in different ways neurons that express different combinations of receptors. Netrin-1 has two separate binding sites on opposite ends, enabling it to simultaneously bind two sensing neogenin molecules on the axons. Neogenin slightly different splice isoforms provide a basis for diverse signalling outcomes (Xu et al. 2014).

Peripheral receptors may have cognitive effects… by themselves! An astonishing piece of evidence shows that sensations are not processed by the CNS, but by peripheral receptors. Most mammals have two types of cone cells: S and M, sensitive to blues and greens. The retinas of Old World monkeys and humans acquired a third cone, sensitive to longer wavelengths (L cone), that allows them to see the red. A group of scientists genetically engineered a strain of knock-in mice that had human L cones in addition to their M and S ones (Jacobs et al. 2007). Animals whose retinas contained both native mouse pigments and human L pigment acquired the capacity to see in combinations of three basic colours, instead of two. Thus the appearance of a new dimension of sensory experience was demonstrated, based solely on gene-driven changes in receptor organization. Unlike the malleable cortex of young animals, adult brains are far more rigid and tend to have a harder time rewiring themselves; it came thus a complete surprise that another experiment endowed adult squirrel monkeys—lacking L cones—colour vision (Mancuso et al. 2009). The scientists injected retinas with a virus that introduced the human gene for the red-detecting pigment into cone cells. Twenty weeks later, the monkeys began to identify red dots; 2 years later, they remained able to distinguish all colours. These remarkable experiments reveal that phenomenal knowledge is an intrinsic property of the peripheral receptor. Receptors have thus a prominent role in sensory pathways and the importance of cortical areas in perceptual synthesis needs to be properly contextualised in terms of the embodied interactions with the world (and internal millionaire) through sensory organs.

In summary, this section has emphasised that neuronal processing cannot be considered in isolation from an embodied neuronal infrastructure—including its own physical substrates. The examples chosen here show that nearly every aspect (from gut bacteria to peripheral receptors) of the embodied nervous system has a profound influence on the nature of neuronal computations and the implicit information processing. The final section considers the implications for the CNS itself in terms of its neuroanatomy and physiology.

Are neurons different from each other? A new phrenology

Some authors claim that each region of the neocortex represents an independent organ, dedicated to a complete and distinct function. This idea, first put forward by the phrenologists Gall and Spurzheim, is still tangible in many current mapping studies aimed at localizing functions—commonly referred to as functional segregation specialisation. Such functional cartography with the aid of neuroimaging techniques has been characterized as "neophrenology" (Nieuwenhuys et al. 2008). In our paper we go further, towards a novel phrenology: the cerebral cortex is composed not only of discrete organs or regions, but of distinct and unique neuronal assemblies that span the macromolecular to microcircuit scale.

Growing evidence confirms that cortex is not homogenous; all areas are not composed of a basic repeated circuit (Elston and Rockland 2002). The cortex has distinct regional variations in the structure of its circuitry and cellular components; it is not a simple assembly of the same canonical microcircuit, whose function depends solely on the axonal connections among them. Indeed, cortex is a collection of deeply heterogeneous cell assemblies. Rather than forming mere functional networks of cells transmitting an electromagnetic impulse, pyramidal neurons, inhibitory interneurons, astrocytes show morphological and biochemical variations (Haustein et al. 2014).

Several studies have revealed distinct specialisations in pyramidal cell phenotype and structure in different cortical layers and areas (Spruston 2008). As an example, the functional columnar organization of sensory cortices, once thought to be underpinned by a network of structurally uniform columns of neurons, clearly shows a different pattern: the number of neurons can differ markedly between the "barrel" columns in the vibrissal area of the rat somatosensory cortex (Yates 2013). These variations are not random, but systematic; that is, cells become more branched and more spinous when comparing primary sensory with sensory association and executive cortical areas. The extent of regional differences in cell structure is species dependent (Elston and Rockland 2002) and the distinct regional specifications are probably due to strict genetic constrains (Spruston 2008; Anderson and Coulter 2013; Southwell et al. 2014; Zhang 2004).

The more we investigate, the more we discover different roles and abilities in apparently homogenous populations

of neurons. We now list some recent studies linking neuronal types to specific active molecules and well-defined behaviours:

- A new neuron type within the area pretectalis helps zebrafish coordinates their eye and swimming movements, to compensate for self-motion (Kubo et al. 2014). These neurons are prevalently direction selective, either monocularly or binocularly driven, and hierarchically organized to distinguish between rotational and translational optic flow.
- Researchers have identified two types of neurons that enable the spinal cord to control skilled forelimb movement. The first is a group of excitatory interneurons needed to make accurate and precise movements; the second is a group of inhibitory interneurons necessary for achieving smooth movement of the limbs (Azim et al. 2014).
- With help from EyeWire, an online community of "citizen neuroscientists", it has been demonstrated that Off-type starburst amacrine cells in retina have dendrites with receptive fields oriented in space–time and therefore respond selectively to stimuli that move in the outward direction from the soma (Kim et al. 2014a, b, c).
- Researchers revealed a specific cell type and microcircuit underlying disinhibitory control in cortex and demonstrated that it is activated under specific behavioural conditions (Pi et al. 2013).
- De novo memory-involved protein expression can be restricted to specific neurons within a population, and to specific dendrites within a single neuron (O'Donnell and Sejnowski 2014).
- Mice virgin males—genetically impaired in vomeronasal sensing—exhibit an odd behaviour: they are parental and do not attack pups as usual. A subset of galanin-expressing neurons in the medial preoptic area is specifically activated during male and female parenting, while a different subpopulation is activated during mating. Thus, galanin neurons emerge as an essential regulatory node of male and female parenting behaviour and other social responses (Wu et al. 2014).
- Large proportion of prefrontal cortex neurons are multifunction, mixed selectivity neurons, specialized for one judgment or the other. They may be crucial in promoting complex, flexible behaviour (Cromer et al. 2010; Rigotti et al. 2013).

The complexity and cellular heterogeneity of neuronal circuitry presents a major challenge to understanding the role of discrete neural populations in controlling behaviour (Ekstrand et al. 2014). While neuroanatomical methods enable high-resolution mapping of neural circuitry, these approaches do not allow systematic molecular profiling of neurons based on their connectivity. New techniques may shed new light on these topics. For instance, it has been recently discovered that associative learning in the mouse is dynamically regulated by the stimulus-specific activation of two distinct disinhibitory microcircuits through precise interactions between different subtypes of local interneurons: in basolateral amygdala, interneurons expressing parvalbumin and somatostatin bidirectionally control the acquisition of fear conditioning (Wolff et al. 2014). Furthermore, as an example, a novel approach identified a number of markers specific to VTA dopaminergic projection neurons (Ekstrand et al. 2014).

Just as activity of individual neurons means different things in different brain areas, so does activity of other cells in CNS. Recent results have redefined microglia and help us to understand how different myeloid cell populations operate, based on their cell-specific gene expression signatures, distinct ontogeny and differential functions. This raises the possibility that astrocytes are not all the same and may serve various roles throughout the different areas of brain (Haustein et al. 2014). Humans also have more types of GABAergic interneurons than other model species—and studies are beginning to show differences in function (Clowry 2014).

Concluding remarks

Our brief theoretical account could be summarized with a seemingly antithetical definition: "supramolecular phrenology". The term "supramolecular" refers to the basic sentiment that information processing should be generalized to cover all metabolic and synaptic signalling in the brain, including the molecular basis of synaptic plasticity. We emphasize the dynamic coordination of information transfer in terms of action potentials contextualizing the exchange among cortical areas (as opposed to the content of the information). Furthermore, we place a holistic emphasis on macromolecules and molecular processes in encoding information. This seems consistent with the information encoded in synaptic connections that accumulates experience with the world through synaptic plasticity. In one sense, it highlights the distinction between perceptual inference (that is contextualised by action potentials) and perceptual learning (that relies upon macromolecular information storage) (Friston, personal communication).

On the other side, the term "phrenology" emphasizes the delicate and heterogeneous nature of cortical hierarchies with deep structure. This fits comfortably with hierarchical predictive coding and functional specialization in the brain, which again emphasizes the distribution of information coding over multiple levels and timescales. This

paper has tried to substantiate the importance of considering the circular causality or reciprocal interactions between separable scales—and between the nervous system and the world in which it is embodied. A proper consideration of this holistic aspect of information processing in the brain may necessarily rest upon a supramolecular phrenology, which can be construed as the ultimate form of embodied cognition.

Acknowledgments I would like to thank Karl Friston for commenting upon an earlier version of this manuscript.

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