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Review article

Neural coding: A single neuron's perspective

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ABSTRACT

What any sensory neuron knows about the world is one of the cardinal questions in Neuroscience. Information from the sensory periphery travels across synaptically coupled neurons as each neuron encodes information by varying the rate and timing of its action potentials (spikes). Spatiotemporally correlated changes in this spiking regimen across neuronal populations are the neural basis of sensory representations. In the somatosensory cortex, however, spiking of individual (or pairs of) cortical neurons is only minimally informative about the world. Recent studies showed that one solution neurons implement to counteract this information loss is adapting their rate of information transfer to the ongoing synaptic activity by changing the membrane potential at which spike is generated. Here we first introduce the principles of information flow from the sensory periphery to the primary sensory cortex in a model sensory (whisker) system, and subsequently discuss how the adaptive spike threshold gates the intracellular information transfer from the somatic post-synaptic potential to action potentials, controlling the information content of communication across somatosensory cortical neurons.

1. Introduction

The principal function of a neuron is to process and communicate information. To achieve its goals each neuron integrates information across thousands of its synaptic inputs. A mechanistic understanding of neural information processing in subcellular resolution will ultimately require quantification of the spatio-temporal distribution of synaptic inputs across the dendrites and soma as distinct neural regions integrate information differently. Previous work has shown that synaptic inputs arriving on the same dendritic branch are integrated in a nonlinear fashion. On the other hand inputs arriving on different branches, or in the soma, are integrated mostly linearly (Major et al., 2013; Mel et al., 2017; Polsky et al., 2004), where the residual nonlinear component is primarily due to reversal potential and conductance changes (see (Cazé et al., 2013) for the principles of nonlinear integration in passive dendrites). In the neocortex, due to the fact that each neuron receives monosynaptic inputs from a few thousand presynaptic partners, often located in distinct brain regions (DeFelipe and Fariñas, 1992), it has not been possible to systematically address the nature of information processing, transfer and recovery in subcellular resolution. However, it is now possible to systematically address the principles of intraneuronal information transfer in single neurons in vitro; whole-cell intracellular recordings from the soma are feasible, and new computational methods

allow the quantification of information flow from somatic post-synaptic potentials (PSP) to action potentials (APs or spikes) after modeling the synaptic input as a response to a hidden state (Zeldenrust et al., 2017), thus reducing the experimental burden in prolonged recording sessions.

Sensory systems offer unique opportunities to study information processing in neural circuits. If the primary function of the sensory circuit is to faithfully and reliably represent the environment, a substantial fraction of the sensory information in the periphery should be represented throughout the sensory circuits. Furthermore, since sensory systems are commonly organized in the form of topographical maps, where sensory receptors in the periphery are represented by topographically organized groups of neurons along the sensory axis, at least part of the sensory information is spatially filtered by the structural organization of the sensory nuclei (Celikel and Sakmann, 2007; Feldman and Brecht, 2005; Kole et al., 2018; Pienkowski and Eggermont, 2011; Schreiner and Winer, 2007; Stewart et al., 2013; White and Fitzpatrick, 2007). In the visual system, for example, projections of retinal ganglion cells target the primary visual cortex (V1) via the lateral geniculate nucleus in an orderly fashion, such that adjacent spots on the retina are represented by adjacent (clusters of) neurons in the lateral geniculate nucleus and the primary visual cortex, thus forming a retinotopic map. Similar types of topographic maps can be found in other sensory systems as well (Kole et al., 2018). A

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prominent example of the topographical maps is the representation of the whisker pad along the brainstem, thalamus and cortex in whisking rodents' brains. This structured organization between the sensory receptors in the periphery and the neurons in the central nervous system allows precise mapping of the origins of the sensory information each neuron receives and the nature of information transfer along the somatosensory axis (see the section on *information transfer along the somatosensory axis*).

Information transmitted between neurons is encoded in the rate and/or timing of action potentials by the presynaptic neuron, although information across the rate and timing is not necessarily redundant. Single unit recordings in the rodent somatosensory cortex, for example, suggest that the timing of APs is more informative than their rate for determining the position of an object in space through whisking, although the information in AP rate might gradually increase for several tens of milliseconds following whisker contact, due to the stimulus evoked long-latency spikes (Panzeri et al., 2001). Furthermore, changes in relative AP timing, but not in its rate, alter the efficacy of monosynaptic connections in the same barrel cortical intracolumnar network (Celikel et al., 2004), contributing to the experience-dependent reorganization of the topographical maps (Kole et al., 2018). Despite the importance of modulated changes in AP rate and timing for encoding sensory information and reorganization of neural circuits, mechanisms that control AP rate and timing are not completely understood. Here we argue that the adaptive nature of the action potential (spike) threshold has a modulatory control over intracellular information transfer, from somatic PSPs to action potentials, and thus shape the information transfer in both AP rate and timing across synaptically coupled networks. Functional consequences of such an adaptive control over AP generation are likely to include the enhancement of stimulus discriminability and membrane state invariant representations of the stimulus (Huang et al., 2016).

2. Information transfer along the somatosensory axis

Whisking rodents are short-sighted nocturnal animals. In particular in darkness they rely on active whisking of their mystacial vibrissae (also known as macro vibrissae or whiskers) to gather sensory information from their environment (Vincent, 1912). The frequency and amplitude of whisker palpations onto tactile targets are modulated based on the recent/current sensory information as well as the contextual requirements of the task, as animals adapt the position of their whiskers based on their expectations about the target location (Celikel and Sakmann, 2007; Voigts et al., 2015, 2008).

Whiskers are specialized (sensory) hairs (Vincent, 1913). Similar to any other hair in the body, they do not contain any sensory receptors. The displacement of the membrane around the hair surrounding the whisker (the follicle) causes the activation of mechanoreceptors in the skin, which leads to the bottom-up propagation of the sensory information from the periphery during whisking (Sofroniew and Svoboda, 2015). The likelihood, duration and rate of the mechanoreceptor activation can be influenced by a number of behavioral variables generated by the animal as motor control signals; alternatively the mechanoreceptor activation can be modulated by the sensory stimulus as the material (e.g. stiffness) and textural properties of the stimulus alter the force transmitted through the whiskers (Fig. 1).

Information originating from whisker touch propagates along a trisynaptic network into the primary somatosensory cortex via major nodes in the brain stem, thalamus and the parietal cortex (Fig. 2; see (Bosman et al., 2011; Diamond et al., 2008; Kleinfeld et al., 1999) for detailed reviews on the anatomy of the circuit). Neurons in the trigeminal ganglion (TG) are silent as long as whiskers remain stationary and their firing rate during whisker motion is modulated by whisking frequency and whisker contact (Leiser and Moxon, 2007). Thus, whisker motion, whisk frequency and contact information are available in the spiking of the TG neurons with a 1–2 ms latency after contact

information reaches the mechanoreceptors. Heterogeneous response properties of the TG neurons suggest that already in the first stage of neuronal processing there is a parallel encoding of different sensory features. The existence of functional subclasses (including neurons that encode whisking, contact with an object, pressure against an object and the detachment from the object (Szwed et al., 2006, 2003)), argue that TG neurons represent unitary features of the sensory information on whisker contact (Fig. 2A); while whisking-responsive neurons report the actual whisker position with high precision, touch-responsive neurons encode the horizontal and axial coordinates of the whisker contact (Derdikman et al., 2006a).

Neurons across four distinct TG subnuclei in the brainstem are the recipient of monosynaptic input from the mechanoreceptors (Fig. 2A). As a result whiskers are represented as four separate topographical maps in the brainstem (Belford and Killackey, 1979; da Silva et al., 2011; Ding et al., 2003; Erzurumlu et al., 2010). Direct comparison of the spike patterns of neurons in two major prominent brainstem nuclei, i.e. the principal nucleus of the trigeminal nuclei (PrV) and subnucleus interpolaris (SpVi) showed that the functional representation of touch is similar across the two nuclei, as neurons in both regions reliably decode stimulus onset, contact duration and frequency at least up to 11 Hz without any adaptation (Sosnik et al., 2001). Representation of touch across spinal trigeminal subnuclei pars oralis (SpVo) and caudalis (SpVc) are yet to be studied systematically.

Ascending projections that target the cerebral cortex, and originate from the brainstem nuclei, are organized into three trigemino-thalamo-cortical pathways (Fig. 2A), each coding different aspects of whisking and touch: while the lemniscal pathway conveys both whisker motion and whisker contact information, the extralemniscal pathway carries information about whisker contacts and the paralemniscal pathway conveys information about whisking (Diamond et al., 2008; Kleinfeld et al., 2006).

Thalamic neurons are functionally diverse with broad receptive fields, many responding equally strongly to different single whisker deflection (Brecht and Sakmann, 2002a). In VPM, ∼25% of neurons encode whisking velocity, while other neurons are sensitive to position, acceleration, or other kinetic features of whisker motion (Fig. 1; (Petersen et al., 2008)). About 19% of VPM neurons encode multiple stimulus features (Petersen et al., 2008), plausibly due to the convergence of brain stem projections, suggesting that a combinatorial representation of the stimulus space can be achieved in single neuron resolution in the thalamus. Information conveyed in VPM neurons' spiking about the stimulus is considerably higher than what barrel cortical neurons communicate to their postsynaptic partners via action potentials (see (Montemurro et al., 2007) for VPM and (Panzeri et al., 2001) for the barrel cortex). A small number of VPM neurons, firing only a few spikes each, could distinguish a large number of stimuli in the periphery, although the information content of VPM spiking is likely to depend on the whisking frequency and in the rate of adaptation of thalamic neurons' firing (Sosnik et al., 2001).

The other primary somatosensory thalamic nucleus that is crucially involved in trigemino-thalamo-cortical information processing is the POM (Fig. 2A). Unlike VPM, the majority of the POM afferents originate from the barrel cortex, and POM does not contain a topographic anatomical map of the contralateral whisker pad (Ahissar et al., 2000; Diamond et al., 1992a, 1992b; Masri et al., 2008). With descending sensory information from S1 and efferent projections to M1, POM is likely to be involved in sensorimotor integration (Masri et al., 2006). Inactivating the barrel cortex largely eliminates the PoM's activity (Diamond et al., 1992a; Ghazanfar et al., 2001). This dependence on the barrel cortical activity might contribute to the phasic regimen of the spiking in the POM that shows strong frequency dependent modulation in rate and timing of action potentials (Sosnik et al., 2001).

The three trigemino-thalamo-cortical pathways converge in the barrel cortex, although their terminals remain spatially segregated (Fig. 2B). This connectivity pattern ensures that barrel cortical neurons
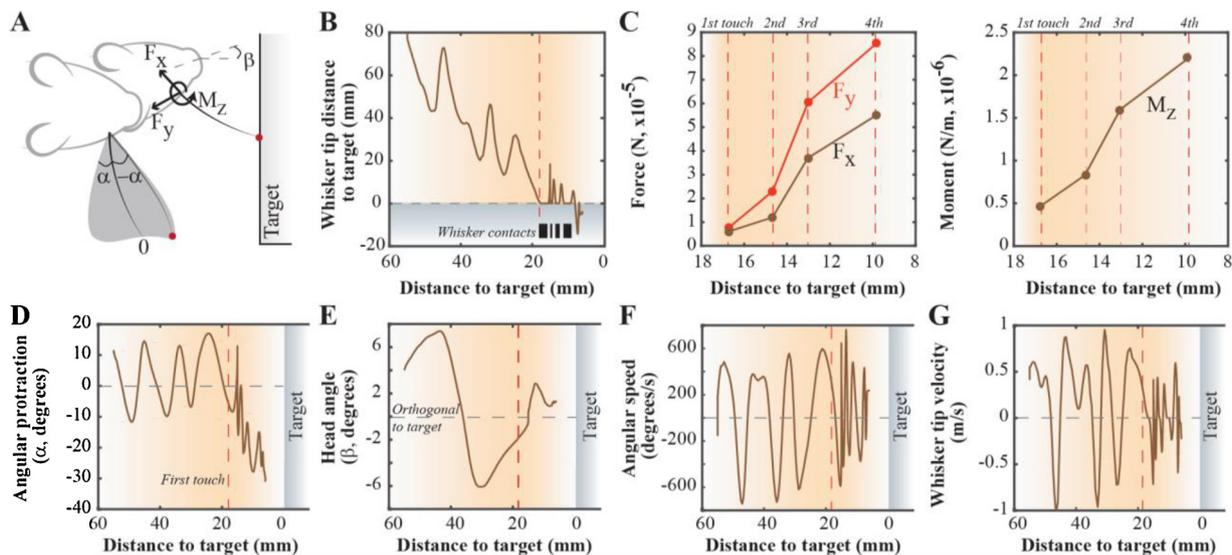
Fig. 1. Principal behavioral variables that shape the sensory information on whisker contact. (A) Whisking rodents employ amplitude and frequency modulation to actively control the position of their whiskers during tactile navigation (Voigts et al., 2015). Red dots denote the whisker tip; α is the angular displacement from the mid-point between the most retracted (i.e. retraction set-point, α) and protracted positions (protraction set-point, -α) of the whisker during whisking; β is the head angle with respect to the plane orthogonal to the tactile target. Whisker contacts with objects in the plane of whisking change the axial force (F_x), transverse force (F_y) and the reaction moment (M_z) at the whisker base, and leads to mechanoreceptor activation to initiate bottom-up propagation of the sensory information. **(B)** Relative distance of a whisker tip to the tactile target during an example free-whisking trial (Azarfar et al, revised). Note that the amplitude of whisking is reduced as the animal approaches the target (Voigts et al., 2015). **(C)** Mechanical force and moment at the whisker base during contacts with the tactile target (Quist and Hartmann, 2012). **(D)** First contact with the target results in a rapid reduction of the whisking amplitude as animals position their whiskers more rostrally (Voigts et al., 2008). **(E)** The head angle with respect to the target varies as a freely moving animal explores a stationary tactile target. Whisker contact with the target causes the animal to reorient its body towards the target (Arkley et al., 2014; Towal and Hartmann, 2006). **(F)** The angular speed of whisker retraction (positive values) and protraction towards the target (negative values) is modulated upon contact. With an increasing number of whisker contacts the animal gradually slows its whisking speed (Voigts et al., 2008). **(G)** Slower whisking changes the scanning speed of the whisker tip upon the first contact (Voigts et al., 2008). Data for the descriptive plots are from an adult rat performing the gap-crossing task (Celikel and Sakmann, 2007; Jenkinson and Glickstein, 2000), where freely moving rodents locate a stationary tactile target in darkness (Azarfar et al, revised) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

can respond to both whisker motion attributes and whisker contact information. Because the sensory evoked responses are modulated by the frequency of whisker displacement (Ahissar et al., 2001; Derdikman et al., 2006b), sensorimotor variables are jointly represented in the spiking of single barrel cortical neurons.

The principal input layer of the barrel cortex, Layer (L) 4, generates the earliest action potentials across the six cortical layers. It consists primarily of excitatory spiny stellate neurons, interneurons constituting only ~8% of the L4 population (Lefort et al., 2009). Sensory evoked activity is first observed 6–8 ms after the stimulus onset, and 2–4 ms after VPM spiking (Allen et al., 2003; Bruno and Simons, 2002; Celikel et al., 2004; Foeller et al., 2005; Pinto et al., 2003). Single L4 neurons
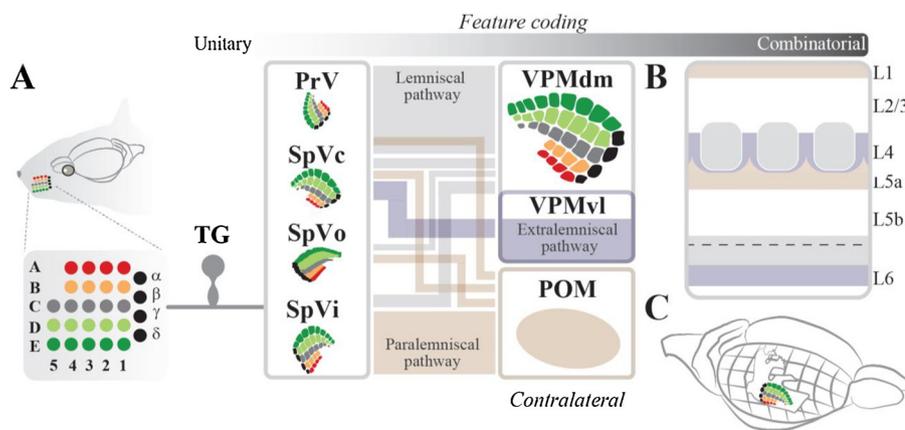
Fig. 2. The whisker-to-barrel cortex pathway encodes, transforms and transfers the sensory information from the periphery to the cortex. This somatosensory axis creates the neural representations of the tactile world. (A) Whiskers on the snout are organized in an orderly grid of 5 rows and 3 - ~8 columns. Rows are named after the first 5 letters of the Latin alphabet and columns are numbered. In addition, a column of (straddler) whiskers are caudally positioned behind the 1 st column, between whisker rows, which are named after Greek letters. Neurons in the trigeminal ganglion (TG) are specialized neurons without dendrites, but with bifurcated axonal branches; the rostral branch terminal transfers the mechanical information via the caudal branch into four subnuclei of the brainstem (PrV, SpVc, SpVo, SpVi). Representations in the brainstem preserve the topography of the whisker pad to various extent, creating four distinct anatomical representations of the whisker pad. Ascending cerebral projections from the brainstem are organized into lemniscal, paralemniscal and extralemniscal pathways that travel, via distinct thalamic subnuclei, into the contralateral hemisphere before ultimately reaching the primary somatosensory cortex (S1). Projections originating from the multi-whisker relay cells in barreloid "heads" in the ventral posteromedial nucleus (VPM) are not shown (Furuta et al., 2009; Urbain and Deschênes, 2007; Veinante and Deschênes, 1999). Whisker representations in the medial division of the posterior nucleus (POM) are not topographical. The size and orientation of the subcortical topographical whisker representations are approximated. VPMdm: Dorsomedial VPM; VPMvl: Ventrolateral VPM. **(B)** The three trigemino-thalamo-cortical pathways terminate in different layers of the posteromedial primary somatosensory cortex, also known as the barrel cortex. Note that the color code specifies the approximate terminal locations for each pathway. For a detailed review see (Feldmeyer, 2012). **(C)** The topography of the whisker representations are preserved in the barrel cortex. The 'Rattunculus' depicts the relative location of the primary somatosensory cortex in the cerebrum as well as the size and orientation of anatomical representations of the contralateral whiskers.

have broad subthreshold receptive fields (Brecht and Sakmann, 2002b) and their suprathreshold receptive fields are smaller than the suprathreshold receptive fields of VPM neurons (Brecht and Sakmann, 2002a). Considering that a relatively larger number of thalamocortical projections converge onto inhibitory neurons (White et al., 1984) and that local inhibitory projections within the L4 sharpen excitatory neuronal responses (Feldmeyer et al., 2018), it is not surprising that L4 neurons represent stimuli with a high spatial acuity and temporal resolution. The spiking of L4 neurons also represents whisker position, although inhibitory neurons carry most of the information on the frequency and location of the tactile stimulus (Reyes-Puerta et al., 2015). During whisking in air, small amplitude, fast fluctuations of the membrane potential of these neurons are correlated with whisker position (Crochet and Petersen, 2006), and the firing rate during whisking is correlated with the amplitude of the whisk cycle (Fee et al., 1997). Although only ~10% of the S1 neuronal population is phase-locked to the rhythmic motion of the whiskers (O'Connor et al., 2002), top-down modulatory input, (e.g. behavioral state (Ferezou et al., 2006) or reward (Ganguly and Kleinfeld, 2004)) could further modulate phase locking. Therefore, the integration of the bottom-up sensory information with top-down contextual information might shape sensorimotor processing already in the earliest stage of cortical processing.

Sensory evoked spiking activity in excitatory neuron populations in the barrel cortex is generally low, especially in the superficial layers (L2/3), a phenomenon believed to be an indication of sparse coding (see e.g. (Barth and Poulet, 2012; Olshausen and Field, 2004; Petersen and Crochet, 2013; Zhao, 2004) for in-depth reviews). Stimulating a single whisker under anesthesia generates only 0.1-0.3 APs/trial in a L4 neuron of the corresponding principal barrel column (Allen et al., 2003; Brecht et al., 2003; Brecht and Sakmann, 2002b; Celikel et al., 2004). The sparseness of the evoked representations is preserved also in L2/3: the deflection of the principal whisker evokes merely 0.03-0.2 spikes/stimulus under anesthesia (Brecht et al., 2003; Celikel et al., 2004), independent from the recording method or the experimental condition studied (Allen et al., 2003; Celikel et al., 2004; Crochet et al., 2011; de Kock et al., 2007; Foeller et al., 2005; Kerr et al., 2007; O'Connor et al., 2010). Although in freely behaving animals firing rates increase about an order of magnitude (Celikel et al., 2004), stimulation of the principal whisker almost always elicits the strongest response, while the representation of the neighbouring whiskers is often weak and unreliable (Brecht et al., 2003; Manns et al., 2004). In agreement with these observations, information theoretic analysis has found that information carried by single neurons' spikes about stimulus location (i.e. which whisker is stimulated) is low (Panzeri et al., 2001; Petersen et al., 2001), since only the response to principal whisker stimulation is somewhat reliable, resulting in whisker touch induced APs only in ~30% of the trials (Celikel et al., 2004). The neurons located in deeper layers generally show higher levels of spontaneous and evoked activity, but the median of the sensory evoked response is still lower than 1 A P/stimulus (de Kock et al., 2007; Manns et al., 2004; O'Connor et al., 2010). This coding principle is not specific to the barrel cortex: neurons in the primary auditory (DeWeese et al., 2003; Hromádka et al., 2008), primary visual (Greenberg et al., 2008; Vinje and Gallant, 2002; Willmore et al., 2011), olfactory (Poo and Isaacson, 2009; Stettler and Axel, 2009) and gustatory (Chen et al., 2011) cortices display similar sparse response properties, suggesting that sparse coding is a general principle employed in sensory processing throughout the sensory pathways (Barlow, 1972; Olshausen and Field, 2004). Sparse coding might impose neural filter properties consistent with the naturally observed ones (Lewicki, 2002; Olshausen and Field, 1996; Smith and Lewicki, 2006).

While the overwhelming majority of the neural population shows sparse response properties, there still exists a small population of neurons that are highly active under anesthesia or in head-fixed animals; they fire reliably when the stimulus is delivered, and usually fire more than one action potentials (Crochet et al., 2011; de Kock et al., 2007;

O'Connor et al., 2010; Yassin et al., 2010). Multiple mechanisms could underlie this highly active neuronal population (Barth and Poulet, 2012): They are possibly strongly wired into the neural circuit (Lefort et al., 2009; O'Connor et al., 2010), receiving stronger excitatory (or weaker inhibitory) drive compared to surrounding weakly active cells. The neuronal intrinsic properties could further shape the probability of spiking (Connors et al., 1982; Nowak et al., 2003). One important question that remains is that whether these highly active neurons are sharply tuned for certain stimuli under specific context, or whether they represent a subgroup of broadly tuned, unselective neurons.

Since the discovery of receptive fields in the visual system (Hubel and Wiesel, 1962), the selectivity of cortical neurons in primary sensory cortices has been well documented. Experimental evidence argues that in the visual (Ohki et al., 2005; Willmore et al., 2011), somatosensory (Andermann and Moore, 2006; Gomez-Ramirez et al., 2014) and auditory (Rothschild et al., 2010) cortices neurons display a high degree of stimulus selectivity, in particular when they are studied using naturalistic, otherwise complex, stimuli (Ramírez et al., 2014; Vinje and Gallant, 2002, 2000) or under specific behavioral contexts (O'Connor et al., 2010). On the other hand several other studies have reported that highly active neurons have broad receptive fields, and contain a high amount of sensory information (Foffani et al., 2008; Ince et al., 2013). Even though random sampling theory suggests that all these experiments should primarily study excitatory neurons (as excitatory neurons outnumber their inhibitory counterparts 6:1 (Markram et al., 2004; Meyer et al., 2011; Petilla Interneuron Nomenclature Group et al., 2008)), in reality extracellular recording methods have biased sampling in favor of neurons that have higher rate of spiking (e.g. inhibitory neurons). Thus, the observed highly active neuron population could be a mixture of neurons that are highly selective to a specific stimulus tested under a given behavioral context as well as neurons that are broadly tuned. Neural recordings in freely behaving animals combined with optogenetic control of targeted cellular populations will help to shed light onto the cellular mechanisms of (sparse) neural encoding of touch.

From the information encoding perspective, high (and heterogeneous) stimulus selectivity of neuronal spiking representations suggests that different neurons might encode distinct stimulus information that is not redundant at the single neuron level. Thus, pooling action potentials from a heterogeneous population ('population code') can often steadily increase the information about the stimulus with the population size. In addition, the correlation structure between individual neurons could significantly affect the population encoding (see (Averbeck and Lee, 2006) for review). The **heterogeneity of stimulus selectivity** suggests that during the decoding process preserving the identities of pooled neurons in a population could maximize the information encoded within the population (Ince et al., 2013). At the population level, **the heterogeneity of response strength** results in the amount of information carried by different neurons to vary significantly as highly active neurons, despite being outnumbered by sparsely active neurons, encode the majority of information in the population in any given trial (Ince et al., 2013). This is consistent with the observation that in many behavioral experiments the spiking response from only a small number of highly active cells can accurately predict the animal's behavior (Mayrhofer et al., 2015; Niessing and Friedrich, 2010; O'Connor et al., 2010; Peron et al., 2015; Stüttgen and Schwarz, 2008).

3. Intracellular information transfer and its quantification

Even though most cortical sensory neurons have sparse *supra*threshold representations, they have reliable and broadly tuned *sub*threshold representations. In the barrel cortex of anesthetized rodents, over 90% of neurons exhibit subthreshold depolarizations upon principal whisker stimulation, and they also respond to the stimulation of more than 8 other surrounding whiskers (Brecht et al., 2003; Brecht and Sakmann, 2002b). Experiments performed in different sensory modalities across
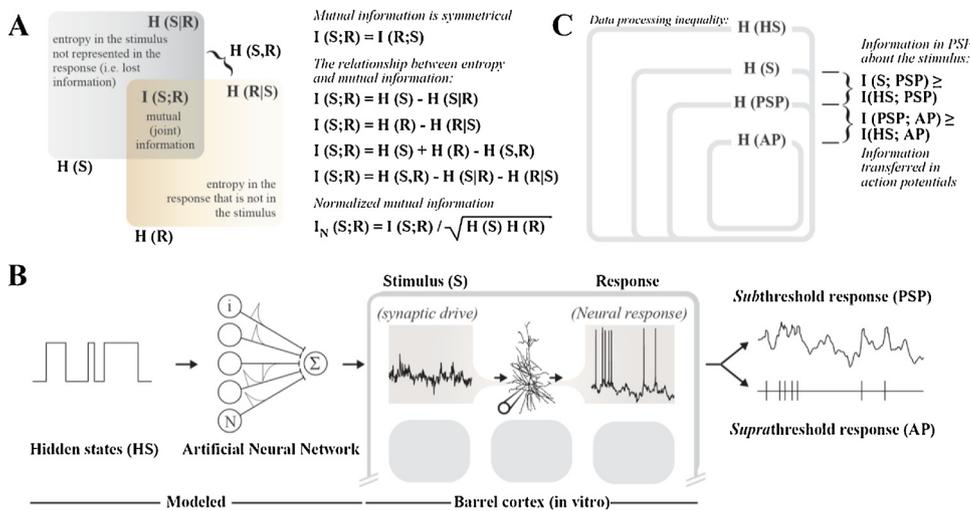
Fig. 3. Quantification of cellular information transfer. **(A)** Mutual information is commonly used to quantify the average joint information between two variables, e.g. stimulus (S) and response (R). The total variability in each variable is termed as entropy (H). The relationship between the entropy and information is graphically shown and algorithmically described. **(B)** Zeldenrust and colleagues (Zeldenrust et al., 2017) have recently introduced a novel approach that enables the quantification of information transfer using limited experimental data. By modeling the synaptic drive of a neuron (stimulus, S) as an output from an artificial neural network, driven by a binary input (hidden state, HS), they reduced the requirement for experimental data without confounding their calculations by the sampling bias (see main text). In whole-cell current clamp experiments this synaptic drive is used to generate neuronal responses that include the subthreshold postsynaptic potential response (PSP) and suprathreshold action potentials (AP). **(C)** Mutual information analysis can be used to quantify the information transfer between any given two (or more) variables. During information transfer in single neurons, novel information cannot be generated, thus the information between the HS and S, PSP or AP gradually reduces ('data processing inequality').

animal states and behavioral contexts show similarly broad subthreshold receptive fields with monosynaptic PSP amplitudes ranging over 2–8 mV per stimulus (Carandini and Ferster, 2000; Crochet et al., 2011; Tan et al., 2004; Volgushev et al., 2000). The broad and efficacious subthreshold representation is in sharp contrast to the sparse and often unreliable representation at the suprathreshold level, and is consistent with the widespread and numerous synaptic connections cortical neurons receive (Bruno and Sakmann, 2006). As a consequence, at the single neuron level, information represented in the subthreshold activity could be much richer compared with that represented in spikes (de Ruyter van Steveninck and Laughlin, 1996; Dhingra and Smith, 2004). This information in the subthreshold response could propagate through the network, even in the absence of spiking, as changes in membrane potential are passed onto neighbouring cells via gap junctions (Galarreta and Hestrin, 2001a, 2001b) and/or by tonically active, membrane potential modulated neurotransmitter release (Rien et al., 2011). Finally, subthreshold signals, especially those generated by large local population activities such as those often measured by LFPs, can capture information about network state changes that cannot be inferred from the spiking activity of a few neurons (Einevoll et al., 2013).

The subthreshold responses can be thought of as the somatic aggregate of the information a neuron receives from its presynaptic network (although the input might have been filtered through the nonlinear dendritic computation mechanisms (Brunel et al., 2014; London and Häusser, 2005; Mel, 1993)), while spikes carry the information each neuron transmits to its postsynaptic partners; thus, an analytical comparison between the two provides a quantitative description of the intracellular information transfer.

Traditionally, the quantification of single-cellular information processing has been done using (variations on) one of the following two methods (see (Borst and Theunissen, 1999) for a review). In the so-called '***direct method***' (de Ruyter van Steveninck et al., 1997; Strong et al., 1998), a time-varying random stimulus is repeated several times; the mutual information between the variables (e.g. stimulus vs response) is calculated based on the response variability, i.e.signal-to-noise ratio (Rieke et al., 1996; Schultz, 2007). However, the requirement for many repetitions, a number that increases exponentially with the number of dimensions in the stimulus, makes the approach impractical for most experimental designs. Secondly, even if there are many trials, this method suffers from a bias due to limited sample sizes (de Ruyter van Steveninck et al., 1997; Nemenman et al., 2004; Strong et al., 1998; Treves and Panzeri, 1995), for which the results need to be

corrected.

In the original method used by de Ruyter van Steveninck & Bialek (Steveninck and Bialek, 1988), a similar time-varying random stimulus is used as in the 'direct method', but instead of many short repetitions, one long stimulus is used. A part of the data is used to fit a (reverse correlation) model, the remaining part of the data is then used to reconstruct the stimulus using this model. From the difference between the real and the reconstructed stimulus, the signal-to-noise ratio and hence the mutual information can be estimated. This method also needs long recording times (typically in the order of hours, depending on the spike rate), due to the need for a relatively large amount of data for model fitting.

Most modern methods of estimating the information transfer are based on one of these two methods: either the response variability is directly estimated or the stimulus is reconstructed by fitting a model, both of which limit the application of these analytical methods in experimental conditions where data cannot be sampled for extended periods of time. For example, during whole-cell intracellular recordings, most experiments need to be completed within an hour, before clamp conditions deteriorate. Thus, the quantification of intracellular information transfer requires novel approaches. Accordingly, Zeldenrust and colleagues (Zeldenrust et al., 2017) have developed a new method where the synaptic input to a given neuron is modeled as an output of an artificial neural network (ANN) responding to a 'hidden state' by firing Poisson spike trains, thereby mimicking all the layers of neural processing before the neuron under consideration. Because of the properties of the ANN (Poisson spike trains, hidden state follows Markov process), the mutual information can be estimated without the need to fit a model or to repeat the stimulus (Fig. 3). This approach considerably diminishes the amount of data needed to the range of minutes, instead of hours, thereby making it possible to measure and compare (intracellular) information processing under varying (e.g. pharmacological, optogenetic, electrical) conditions in vitro.

4. Regulation of information transfer in local networks and single neurons

It has long been speculated that sensory neurons preferentially transmit those messages (spikes) that carry unique information to reduce the redundancy in the transmitted information while increasing the channel capacity (Attneave, 1954; Barlow, 1961). Following this argument, if the subthreshold responses across neurons contain

redundant information, neurons should not transmit all the available subthreshold information to their postsynaptic partners. The nature of the transmitted information could depend on the computation performed by the postsynaptic partners (Felleman and Van Essen, 1991). The excitatory neuron population in L2/3 of rodent barrel cortex, for example, contains two intermingled subpopulations that specifically target the secondary somatosensory cortex (S2) or the primary motor cortex (M1) (Chen et al., 2013; Yamashita et al., 2013). When the animal is actively using its whiskers to palpate an object, the whisker contacts are reliably (but differently) represented in the subthreshold response of both neuronal subpopulations: during an episode of repetitive whisker contacts, M1-projection neurons only spike transiently after the first contact, whereas S2-projection neurons generate spikes (relatively) robustly to each whisker contact (Yamashita et al., 2013). Discrimination analysis further indicates that spikes from M1-projection neurons contain more information about the presence of the stimulus, whereas spikes from S2-projections neurons contain more information about stimulus features (Chen et al., 2013).

What are the neural mechanisms that transform the strong and broadly tuned subthreshold representation into sparse and selective representations of the sensory information in the periphery in the form of action potentials? At the network level, inhibition plays an important role in shaping sensory responses of cortical neurons by suppressing the activity of excitatory neurons (Feldmeyer et al., 2018). Sensory stimulation evokes precisely timed excitatory and inhibitory drives onto cortical excitatory neurons, with inhibition usually being stronger and slightly delayed compared to excitation, which allows a short window of opportunity during which the excitatory drives can summate and drive spiking activity (Gabernet et al., 2005; Okun and Lampl, 2008; Staiger et al., 2009). The inhibitory drive in the network, however, depends on the short-term dynamics of synaptic communication (Feldmeyer et al., 2018). For example, in the barrel cortex transient thalamocortical input onto Parvalbumin (PV+) and Somatostatin (SST+) expressing L4 neurons results in rapid hyperpolarization of their postsynaptic excitatory partners (Tan et al., 2008). During sustained stimulation, while PV+ neurons undergo short-term depression, SST+ neuronal responses facilitate, differentially regulating the inhibitory drive onto the excitatory neurons (Tan et al., 2008).

Alterations in this excitatory to inhibitory balance modulates cellular and network excitability, controlling action potential rate and timing (Juczewski et al., 2016; Miceli et al., 2017). The exact temporal shifts between excitation and inhibition vary across different sensory modalities, ranging from ~1 ms in the barrel cortex (Gabernet et al., 2005) to ~1-4 ms in auditory cortex (Wehr and Zador, 2003), ~10 ms in olfactory cortex (Poo and Isaacson, 2009), and longer in visual cortex (Hirsch et al., 1998). Comparing inhibitory and excitatory receptive fields in the same neuron generally shows that the tuning of inhibitory inputs are either matched (Okun and Lampl, 2008; Wehr and Zador, 2003; Zhang et al., 2003) or broader than the excitatory drive (Liu et al., 2009; Poo and Isaacson, 2009). Furthermore, just a few simultaneously activated excitatory neurons are needed to induce strong and widespread inhibition on the neural network (Kapfer et al., 2007). The sensory evoked inhibition that is strong, widespread and tightly coupled with excitation serves many functions, which include controlling precise timing of the response (Gabernet et al., 2005; Okun and Lampl, 2008; Wehr and Zador, 2003), preventing runaway excitation (Kapfer et al., 2007), sharpening stimulus selectivity (Liu et al., 2009; Poo and Isaacson, 2009; Zhang et al., 2003), and increasing the overall sparseness of sensory response (Haider et al., 2013; Sachdev et al., 2012). Synaptic regulation of inhibition controls network excitability through disynaptic disinhibition (Prönneke et al., 2015), enables spatial summation (Adesnik et al., 2012), controls emergence of gamma oscillations (Cardin et al., 2009), regulates additive and divisive gain modulation (Kvitsiani et al., 2013; Pi et al., 2013), controls sensory adaptation (Natan et al., 2015) and contributes to sensorimotor transformations for whisker positional (motor) control (Sachidhanandam

et al., 2016; also see (Feldmeyer et al., 2018) for an recent review on the organization and function of inhibitory circuits in the barrel cortex).

At the single neuron level, the spike threshold (Koch et al., 1995) can transform a broadly tuned subthreshold response into a sparse and more selective spike response through the so-called 'iceberg' effect (Rose and Blakemore, 1974): since the membrane potential is usually well below the spike threshold, only sufficiently large excitatory input can drive the membrane potential to reach the spike threshold for spike generation, thus generating a more sharply tuned spiking response compared to the subthreshold response. The spike threshold and inhibition work synergistically: inhibition that is tightly coupled to excitation suppresses sensory evoked responses to below spike threshold most of the times. Thus, spikes are only generated sparsely (Huang et al., 2016; Renart et al., 2010). Indeed, whole-cell recordings in head restrained behaving mice have shown that whisker contact reliably drives the neuronal membrane potential to a fixed value, which is independent of the membrane potential prior to whisker contact, and which remains below the spike threshold in most excitatory neurons; on a given trial, only in a small fraction (~10%) of excitatory neurons the contact induces a membrane potential change above the spike threshold, resulting in action potential discharge (Crochet et al., 2011). Inhibition that is more broadly tuned compared to excitation can further sharpen the neuronal selectivity (Liu et al., 2009; Poo and Isaacson, 2009; Zhang et al., 2003). Interestingly, the spike threshold is not fixed but rather depends on the temporal profile of the membrane depolarization, such that fast depolarizations produce spikes at lower thresholds, and slower depolarizations at higher thresholds (Azouz and Gray, 2003, 2000; de Polavieja et al., 2005; Fontaine et al., 2014; Goldberg et al., 2008; Huang et al., 2016; Wilent and Contreras, 2005). It was suggested that increased spike threshold is (at least in part) a result of decrease in Na+ conductances, while spike threshold depolarization enhances spike generation in response to synchronized inputs (Azouz and Gray, 2000). Recently, this assumption was explicitly tested using intracellular recordings from the L2/3 of the barrel cortex and computational simulations (Huang et al., 2016). It was indeed found that using an adaptive threshold, instead of a constant spike threshold, enables robust stimulus encoding. This was in particular true for highly correlated inputs, such as those observed during whisker contact, even if the stimulus induced correlations are confounded by noisy fluctuations of the membrane potential. The information content of the action potentials is preserved even if the membrane undergoes up-down state fluctuations, enabling membrane state-invariant representations of the sensory stimulus (Huang et al., 2016).

5. Outlook: Three foci for the future empirical and computational work

In a network that consists of multiple circuit components, the information flow is dictated by the integration properties of each node, the channel capacity between the nodes and the network connectivity. Excitatory and inhibitory neurons have fundamentally different network formations that shape sensory representations in a cell-type specific manner. For example, sensory evoked spiking activity in interneurons is dense (as opposed to sparse), more reliable and less selective compared to the sensory representations of excitatory neurons (Reyes-Puerta et al., 2015). These differences are partially due to the higher excitability of interneurons, as some interneuron populations have comparable (to excitatory neurons) subthreshold tuning (Bruno and Simons, 2002; Cardin et al., 2007; Nowak et al., 2008; Wu et al., 2008), but cannot be generalized across all different subclasses of inhibitory neurons. PV+ interneurons, for example, have broad receptive fields with strong, unselective and short latency responses to whisker deflections, whereas SST+ interneurons show weak, more selective and delayed responses to visual stimuli (Ma et al., 2010). In the barrel cortex, SST+ interneurons are inhibited by whisker contacts (Gentet et al., 2012). Given the fundamental differences in their network

organization and the differences between sensory representations by excitatory and inhibitory neurons, it is likely that excitatory and inhibitory neuronal populations transfer information in parallel, plausibly encoding and decoding different information in the rate and/or timing of action potentials. Therefore, systemic analyses of intracellular information transfer in a cell type specific manner should unravel the principal building blocks of information flow in networks in single neuron resolution.

The stimulus selectivity of excitatory neurons is maintained in part by network motifs. For example, the visual cortical excitatory neurons form non-random sub-networks, such that neurons selective to the same stimulus features are more likely to connect with each other (Ko et al., 2011). This type of functionally specific connectivity pattern is largely absent at least in the PV + interneuron populations, and experimental evidence suggests that the spiking responses in interneurons are less selective or more broadly tuned ((Bruno and Simons, 2002; Hofer et al., 2011; Liu et al., 2009; Sohya et al., 2007; Swadlow, 1989; Wu et al., 2008) but also see (Reyes-Puerta et al., 2015; Runyan et al., 2010)), and can be approximated by the average tuning of adjacent excitatory neurons (Kerlin et al., 2010). Thus, empirical and theoretical work that will address how different network motifs and coding schemes are used in a state dependent manner to adapt (or control) the information flow will unravel the contextual influences in information processing and transfer in (cortical) networks.

Excitatory and inhibitory neurons are likely to encode different features of the stimulus in their spiking activity. With their high excitability, high sensitivity, broad tuning, short onset latency and reliable and highly synchronized (Swadlow, 2003) stimulus evoked firing, fast spiking PV + interneurons could reliably encode the stimulus onset, whereas the sparse and temporally distributed excitatory neurons' spikes could encode more detailed features of the stimulus. The high firing rates of interneurons could also suggest that they might preferentially employ rate coding. Most decoding analyses based on ideal observers assume that the decoder has the knowledge of stimulus onset timing, whereas in real neural networks it is not trivial for the postsynaptic neurons to access such information. It has been proposed that the peak of the population activity could be used as a temporal reference for decoding (Panzeri and Diamond, 2010); however, given the response properties of PV + interneurons, the response of these neurons could a (better) alternative for a temporal reference for decoders. Determining the reference framework will allow systematic analysis of information processing, loss and recovery in neuronal populations. When how network motifs, coding schemes and temporal reference frameworks determine and shape cortical information flow are determined, the replication of these elementary steps of neuronal information processing in artificial networks will be within reach.

Acknowledgements

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