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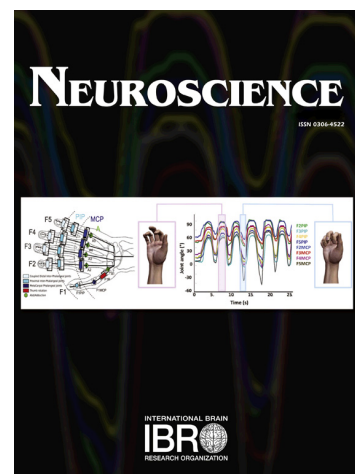
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Representation of tactile scenes in the rodent barrel cortex

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Abstract

After half a century of research, the sensory features coded by neurons of the rodent barrel cortex remain poorly understood. Still, views of the sensory representation of whisker information are increasingly shifting from a labeled line representation of single whisker deflections to a selectivity for specific elements of the complex statistics of the multi-whisker deflection patterns that take place during spontaneous rodent behavior – so called natural tactile scenes. Here we review the current knowledge regarding the coding of patterns of whisker stimuli by barrel cortex neurons, from responses to single whisker deflections to the representation of complex tactile scenes. A number of multi-whisker tunings have already been identified, including center-surround feature extraction, angular tuning during edge-like multi-whisker deflections, and even tuning to specific statistical properties of the tactile scene such as the level of correlation across whiskers. However, a more general model of the representation of multi-whisker information in the barrel cortex is still missing. This is in part because of the lack of a human intuition regarding the perception emerging from a whisker system, but also because in contrast to other primary sensory cortices such as the visual cortex, the spatial feature selectivity of barrel cortex neurons rests on highly nonlinear interactions that remained hidden to classical receptive-field approaches.

Keywords: Barrel cortex, whisker stimulation, naturalistic stimulus, sensory responses, neural coding.

Introduction

In this Review, we describe the wide repertoire of whisker movement features that are coded by barrel cortex neurons in the anesthetized rodent preparation. We start from the low-dimensional properties described with simple single-whisker deflections that can be combined into a linear model of barrel cortex neurons. We then discuss the impact of several elements of the sensory context, such as the stimulation density and the effect of an immediately preceding stimulus, which both affect neuronal responses in ways not predicted by the linear model. These observations reveal the existence of numerous intrinsic nonlinearities of cortical neurons.

Neuronal selectivity for global tactile properties of the surfaces contacted by multiple whiskers cannot be available from any single whisker contact alone. We describe recent efforts to understand how neurons in the vibrissal system analyze simultaneous whisker deflections and how the barrel cortex extracts collective properties of complex stimuli.

1. A receptive field analysis of barrel cortex neurons function

To identify the functional properties of neurons, the traditional approach in sensory physiology has been to explore the sensory periphery and find the limits of the area of the periphery that triggers a neuronal response. Delineating this area – the so called receptive field (Hartline, 1938) – has been a dominant research strategy in the study of the barrel cortex, inspired by the earlier studies of the visual system (Hubel, 1959; Hubel and Wiesel, 1962) that were highly informative of visual functional properties. In the whisker system, the relevant stimulus space includes not only the identity of the stimulated whiskers (Welker, 1971), but also a number of additional parameters of the whisker deflection – including the direction and amplitude of the whisker stimulation – that are encoded by the highly specialized tactile sensors in whisker follicles (Rice 1993, Rice et al., 1993, Mosconi et al., 1993).

1.1: Multiple tunings to specific whisker deflection properties

With the advent of the first controlled single-whisker stimulators, several studies have demonstrated that barrel cortex neurons encode specific properties of whisker deflections. These features include the amplitude of the peripheral movement, either in position, speed or acceleration (Simons, 1978; Simons, 1983; Arabzadeh et al., 2003), the frequency of an oscillatory input (Simons, 1978; Arabzadeh et al. 2003; Andermann et al., 2004; Ewert et al. 2008), the interval between repetitive stimulations (Simons, 1985; Ahissar et al., 2001; Webber and Stanley, 2004) and the direction of deflection (Simons, 1978; Bruno and Simons, 2002; Wilent and Contreras, 2005). These studies have mostly focused on responses to movements of the principal whisker (PW), which is classically defined based on the latency and/or strength of the neuronal response to a standard ramp-and-hold whisker deflection. Similar response properties are observed for stimulation of the surround whiskers that elicit a response, albeit with reduced amplitude and dynamical characteristics.

Among these tuning properties, direction selectivity has been one of the most thoroughly studied, perhaps because it represents the most obvious feature of the input space that can be parameterized and is also a prominent feature of barrel cortex neuronal responses. For example, Figure 1A shows intracellular recordings of a layer 4 neuron in the anesthetized rat in response to deflection of its principal whisker in eight randomly interleaved directions (Wilent and Contreras, 2005). Robust synaptic responses were observed, occasionally leading to one or two spikes. The selectivity to the direction was larger for the spike output than for the synaptic potentials, highlighting the contribution of intracellular mechanisms and spike thresholding to information processing.

Most natural whisker deflections occur at very high speed and acceleration (Ritt et al., 2008), and particularly during discrete stick then slip events (Wolfe et al., 2008) that occur when a whisker is rubbed against a surface. Neuronal recordings have been performed during such events (Jadhav et al., 2009). In a 20 ms time window following slip events, particularly those with high acceleration, the firing rate of the neuron recorded in an awake head-fixed rat is

increased (Figure 1B). Even more systematic and reliable spiking (approximately 1 action potential per event) was observed in the first-order mechanosensory neurons in the trigeminal ganglion of the anesthetized rat (Lottem and Azouz, 2009). These results suggest that a few profiles of whisker motion can trigger the response of a sensory neuron to its principal whisker. Like in the visual system, the signal processing filters through which each neuron analyzes its input can be viewed as elemental neuronal computations.

Recently, several studies have systematically measured the temporal filters of barrel cortex neurons, that is the optimal whisker deflection shape to trigger spikes (Maravall et al., 2007; Estebanez et al., 2012). This has been done by delivering white noise (randomized deflections) to the peripheral inputs while recording the spiking output of a neuron (Figure 1C1). Significant temporal filters are then extracted using reverse correlation techniques such as the spike-triggered average or the spike-triggered covariance, in particular for the principal whisker (Figure 1C2). In the barrel cortex, principal component analysis of significant linear filters obtained from neurons in layers 4 to 6 showed that most individual filters could be described as a linear combination of two 30 ms deflection profiles, called the common filters of the system. These filters are 90° dephased versions of each other (Figure 1C3). These filters are a combination of pure speed and pure acceleration filters, and suggest that barrel cortex neurons may focus on stimulation events that maximize these components such as stick and slip shapes (that turn out to have time profiles that can be directly compared to the filters shapes, Lottem and Azouz, 2009). This speed/acceleration also triggers spiking in layer 2/3 of the barrel cortex (Estebanez et al., 2016; Martini et al., 2017). A full review of the buildup of temporal filters across the different stages of the whisker system can be found in the same volume (Bale and Maravall, 2017).

The relevance of the features identified in anesthetized rodents is confirmed by behavioral studies showing that trained head-fixed animals can accurately decode these parameters in the absence of self-generated whisker movements, including the presence of "slip-like" events (Waiblinger et al., 2015) or the frequency and speed of an oscillatory pattern (Stuettgen et al., 2006; Mayrhofer et al., 2013). Recent results obtained in freely running rats further demonstrate that extraction of tactile information from the environment does not

necessarily rely on active rhythmic whisker motion (Kerekes et al., 2017).

In the behaving rodent, these fine scale touch inputs may be often dominated by large scale whisking (Welker, 1964), which can activate Merkel mechanoreceptors in the whisker follicles (Severson et al., 2017) and get relayed up to the trigeminal ganglion neurons (Campagner et al., 2016). However, inhibitory neurons located in the layer 4 of the barrel-cortex seem capable to filter out the inputs related to the whisker active movements, allowing the transmission of mostly -touch-related inputs to layer 4 excitatory neurons (Yu et al., 2016). Therefore, the stimulus space that is tested in the anesthetized rodent preparation is likely to match the inputs that are actually processed in the barrel cortex of awake behaving animals.

1.2: The receptive field, a collection of single-whisker filters

The discovery, half a century ago, of the discrete anatomy of the barrel cortex (Woolsey and Van der Loos, 1970), and of the precise point-to-point projections at many levels across the pathway from follicles to the cortex, have initially emphasized a fundamentally parallel view of the whisker system (Welker, 1971). At first sight, this sensory processing system could thus seem like a coexistence of labeled lines, each whisker sending information to a given barrelette, barreloid and barrel. However, very early on, functional studies have reported that the firing rate of neurons is increased following movements of more than one whisker (Simons, 1978; Ito, 1981; Armstrong-James and Fox, 1987; Ghazanfar and Nicolelis, 1999).

Figure 2A shows the spatial extent of the receptive field of a neuron in layer 4 of barrel C2 of an anesthetized rat (Le Cam et al., 2011). In addition to the principal whisker, the deflection of neighboring whiskers evokes spiking significantly above the baseline level. Spiking receptive fields can encompass more than 10 whiskers, especially in layer 5b, and tend to be elongated along rows (Simons, 1978; Armstrong-James and Fox, 1987). Intracellular recordings have confirmed these results and extended them to a detailed description of the

subthreshold postsynaptic potentials evoked by stimulation of the principal and neighboring whiskers (Moore and Nelson, 1998; Zhu and Connors, 1999; Brecht and Sakmann, 2002a; Brecht et al., 2003; Manns et al., 2004). In particular, subthreshold membrane potential studies have revealed the existence of "silent" cells in layer 3, which fire very few spikes but receive inputs from whiskers two to three rows away from the PW (Figure 2B, Erchova & Shulz, unpublished results; Brecht et al., 2003). Another interesting property gathered from these intracellular recordings is the relative paucity of inhibitory or suppressive zones in barrel cortex receptive fields. This differs from the thalamic stage, in which both inhibitory potentials and suppression of activity can be demonstrated for deflection of surround whiskers (Brecht and Sakmann, 2002b; Ego-Stengel et al., 2012). The dominance of excitatory responses in S1 is also contrasting with typical receptive fields in the visual system, and could originate in the very fast arrival of excitatory and inhibitory signals in S1 (< 10 ms), those signals being tightly synchronized and correlated in amplitude (Okun and Lampl, 2008).

This neuron-centered view of barrel cortex function can be complemented with a whisker-centered view, using techniques which allow the measure of activity across the surface of the cortex. Indeed, single-whisker evoked activity extends over at least 10 cortical barrels (Figure 2C) as shown by exploring responses across the surface of the cortex (Axelrad et al., 1976), and in later works by recording with electrode arrays the spread of spiking activity in response to the deflection of a single whisker, (Petersen and Diamond, 2000). This finding was confirmed using Voltage-Sensitive Dye Imaging (VSDI), which reveals subthreshold responses (Berger et al., 2007): a single-whisker deflection triggered a large wave of activity originating in the corresponding barrel column, and rapidly spreading throughout the whole barrel cortex and beyond (Figure 2D) (Ferezou et al., 2006; 2007). These results confirm that functional connections allow barrel cortex neurons to gather information from way more than a single whisker and are a possible substrate for the integration of information from multiple whiskers.

Overall, in contrast to the sharp feature selectivity observed at the single whisker level, the spatial organization of barrel cortex receptive fields reveals little consistent structure in their

spatial extent and mostly consists of a number (0-10) of adjacent whiskers in addition to the principal one. Therefore, in contrast to other primary sensory areas such as the primary visual cortex (Hubel and Wiesel, 1962), the first-order structure of the whisker receptive fields suggests that the dominant computation may be a simple averaging of the whisker stimulations occurring over a patch of 1 to 10 nearby whiskers.

2. Beyond the linear receptive field

Compared to the visual and auditory primary sensory cortices, the lack of a sharp spatial structuring of barrel cortex linear receptive fields is perplexing. They generally follow a blob-like shape (Brecht and Sakmann, 2002b; Brecht et al., 2003; Manns et al., 2004; Moore and Nelson, 1998; Zhu and Connors, 1999) and there is little indication that such receptive fields may support a complex spatial feature extraction mechanism such as ON/OFF fields (Le Cam et al., 2011). This observation suggests either that barrel cortex neurons only perform simple averaging of the stimulus intensity observed across nearby whiskers, or that more complex spatial computations are performed in the barrel cortex but can only be unveiled by looking beyond the classical linear receptive field.

Rats and mice rarely, if ever, have their whiskers deflected individually during behavior. Rather, during active exploration, animals control the acquisition of sensory information by moving their head and their whisker arrays in a goal-directed manner to collect relevant information (Mitchinson et al., 2007; Grant et al., 2009). Because of these strategies of information collection, animals encountering objects or running past surfaces have many of their whiskers on one or both sides deflected simultaneously. Some components of these deflections are strongly synchronized across the pad, while others are independent. Moreover, the inputs on each whisker follow complex time courses distributed over many frequencies, often looking like "noise", and never repeating in exactly the same way upon repetitive scanning of the same surface (Boubenec et al., 2014). One direction of research consists in characterizing common elements and statistics of these highly complex spatiotemporal patterns of contact. For example, this approach has revealed the dominant

temporal sequences of whiskers ordered by their first touch during exploration of a flat surface (Hobbs et al., 2015).

In the visual system, the principles of organization of visual receptive fields have been successfully reconstituted from the knowledge of the natural stimulation statistics (Atick, 1992; Olshausen and Field, 1996). This approach could potentially lead to similar insights in the whisker system. However, we have learned from decades of investigations in the visual system that such an approach is challenging and presents many obstacles to overcome (Rust and Movshon, 2005).

This difficulty is particularly true for the whisker system. Even if multi-whisker natural stimuli are likely to constitute a relevant subset of all possible stimuli, the task of characterizing quantitatively natural tactile scenes in the context of the rodent vibrissal system is far from trivial and is in itself the object of intensive research efforts (Hartmann, 2011). In addition, in contrast to the visual system, cortical tactile responses are highly nonlinear and dependent on the statistics of the stimulation, and call for a tight control of the sensory context in which sensory responses are probed (Maravall et al., 2007; Ramirez et al., 2014; Estebanez et al., 2012). This tight control is best obtained when using artificial whisker stimulation sequences. Therefore, even if ultimately the goal is to understand the responses to natural tactile scenes, synthetic multi-whisker stimulation paradigms built from artificial single-whisker deflections have been largely predominant in the study of the barrel cortex.

In the following sections, we first describe the means to apply independent deflections on multiple whiskers simultaneously – a prerequisite to study multi-whisker integration. We then review a large body of studies that have characterized several simple spatial and temporal nonlinearities revealed with carefully designed stimulation patterns, based on the features observed during spontaneous behavior.

2.1: Generating complex tactile stimuli for a thorough exploration of the rodent whisker system

Deflecting identified whiskers by hand is the most immediate way to generate sensory stimulations in the whisker system of the anesthetized animal (Welker, 1971), and is thus a practice still in use today to estimate the receptive field of a neuron in preparation for further investigations (Whitmire et al., 2017). Similarly, applying air puffs on the whisker pad is a straightforward way to obtain multi-whisker stimulations (Hutson and Masterton, 1986; Nunez et al., 1994; Brecht and Sakmann, 2002a; Jouhanneau et al., 2015). However, the accuracy and the constancy of this global stimulation are not well controlled. In contrast, the systematic deflection of each whisker in a controlled way has required the development of specific tools exclusively for this goal, since whisker stimulation requires large and fast movements that are not attainable with conventional mechanical actuators. Early technologies for whisker stimulation included galvanometric actuators (Simons, 1978) that allowed precise movements but at the expense of sufficient accelerations (Ito, 1981), although recent galvanometer-based actuators have largely solved this issue (van der Bourg, 2016). Another choice is loudspeaker-derived whisker deflectors (Figure 3A) that met many requirements but were unable to produce accurate positioning of the whiskers beyond the two end-stops of the solenoid (Chapin, 1986; Ghazanfar and Nicolelis, 1999; Krupa et al., 2001). More recently, most of the community has settled on using piezoelectric “benders” (Simons, 1983). These actuators are made of two sheets of piezoelectric material that perform a differential sheering action under an electric field. These device can produce angular deflections up to 1500 degrees per second (Simons and Carvell, 1989) and up to a few degrees of whisker deflection range. More importantly, this technology allows broadband and micrometer-accurate playback of naturally occurring whisker deflection sequences (Jacob et al., 2010), and can be extended from a 1D to 2D deflection space (Figure 3B-C; Simons, 1983; Andermann and Moore, 2006; Jacob et al., 2010; Ramirez et al., 2014; Estebanez et al., 2016).

Beyond single whisker stimulation, neurophysiologists have attempted early on to control separately the deflection of multiple whiskers, in order to study how the cortical activation recorded during single whisker deflections combine during parallel deflections of multiple whiskers.

The development of the required multi-whisker stimulators has been a demanding task because of the complex geometry of the whiskerpad (Towal et al., 2011; Brecht et al., 1997; Jacob et al., 2010). This implies the need to assemble a set of independent stimulators converging into the approximate 1 cm² of the rat whisker pad. Still, multi-whisker stimulators have been progressively developed that allow the independent stimulation of 5 whiskers (Simons, 1985; Brumberg et al., 1996; Rodgers et al., 2006), 9 whiskers (Drew and Feldman, 2007; Andermann and Moore, 2006; Ramirez et al., 2014) and finally 16 to 24 whiskers (meaning that most of the macrovibrissae are stimulated, Krupa et al., 2001; Jacob et al., 2010; Figure 3A).

In our laboratory, we have designed a flexible and compact piezoelectric holder which can be packed in a 5x5 matrix arrangement (Jacob et al., 2008). We have developed a software solution to allow the delivery of deflection signals up to 1000 Hz with minimal ringing artifacts (less than 5% of the total amplitude) (Jacob et al., 2010). With this new generation of multi-whisker device, we can thus deliver complex spatiotemporal patterns of whisker deflections in all directions with high-frequency content, even on the very compact whisker pad of the mouse, and therefore combine complex tactile input with an easy access to modern genetic tools (Figure 3C).

2.2: Nonlinear integration of simple deflection sequences

Nonlinearities in the cortical processing of tactile inputs were first observed in the seminal work of Simons (1978). During sinusoidal oscillatory single whisker deflections in anesthetized rats, Simons observed that most regular spiking units responded mainly to the onset of the stimulation and progressively decreased their response to subsequent stimulation. This phenomenon of rapid sensory adaptation to repetitive whisker stimuli (Figure 4A) has been further characterized by many studies (for review see Whitmire and Stanley, 2016; Lampl and Katz, 2017). Interestingly, its appearance seems to coincide developmentally with the acquisition of exploratory whisking (Borgdorff et al., 2007; Grant et al., 2012; Arakawa and Erzurumlu, 2015).

Rapid sensory adaptation can be observed both in the trigeminal nuclei (Mohar et al., 2013; Mohar et al., 2015) and in the thalamus (Ahissar et al., 2000; Sosnik et al., 2001; Ganmor et al., 2010). Nonetheless, the depression of thalamocortical synaptic transmission is likely to be a major determinant of this sensory adaptation. Indeed, simultaneous recordings from the VPM and the barrel cortex during repetitive stimulation of the principal whisker revealed modest adaptation in the thalamus, but a rapid and strong suppression of both subthreshold and suprathreshold responses at the cortical level (Figure 4A, Chung et al., 2002). The same study also showed that responses to cortical microstimulation were not affected by adaptation to the repetitive principal whisker deflection, suggesting that adaptation does not rely on a change in the efficacy of intracortical synapses. Within the cortical layer 4, classically seen as the major thalamo-recipient compartment, sensory adaptation has been shown to vary according to the recorded cell type (Brecht and Sakmann, 2002; Khatri et al., 2004; Gabernet et al., 2005), indicating that the thalamo-cortical synaptic transmission is target-specific as reported in other cortical connections (Reyes et al. 1998; Rozov et al. 2001).

The brain state, and more specifically the thalamic firing mode, strongly impacts sensory adaptation, which cannot therefore be considered as a fixed property of the bottom-up flow of information (Castro-Alamancos, 2004; Whitmire et al., 2016, 2017). Sensory adaptation leads to a shrinkage of the receptive field, as revealed by repetitive stimulation not only of the principal whisker but also of adjacent whiskers (Figure 4B, Katz et al., 2006). This observation is indeed consistent with the reduced spatial extent of adapted cortical responses (Kleinfeld and Delaney, 1996; Sheth et al., 1998; Ollerenshaw et al., 2014). Such sharpening of cortical responses (Figure 4C) suggests that the adapted state could improve the ability to discriminate finer features of the tactile scenes (Ollerenshaw et al., 2014; Musall et al., 2014). Furthermore, this rapid stimulus-specific sensory adaptation (Katz et al., 2006; Musall et al., 2014, 2017) might be fundamental to extract behaviorally important information from a background of constantly varying sensory inputs (Whitmire and Stanley, 2016).

Interactions between spatially separate components of the receptive fields have been

studied in other sensory modalities (Heggelund, 1981; Sillito et al., 1995; Lampl et al., 2004) in order to identify nonlinearities of spatial integration. In the barrel cortex, the discrete whisker grid defines a natural way to split spatially the receptive field. It is thus particularly straightforward to compare the responses to separate whiskers versus the response to a stimulation that combines the selected whiskers. When recording the neuronal responses to deflections of pairs of whiskers with varying delays, mainly suppressive interactions have been reported (Simons, 1985; Carvell and Simons, 1988; Simons and Carvell, 1989; Kleinfeld and Delaney, 1996; Goldreich et al., 1998; Mirabella et al., 2001; Higley and Contreras, 2005, Erchova et al. 2006). Both sub-cortical and intracortical processes are thought to contribute to such sublinear integration of multi-whisker input. However, at odds with these observations, some supralinear interactions have also been reported in supra (Figure 4D) and infra granular layers of the barrel cortex (Ghazanfar and Nicolelis, 1997; Shimegi et al., 1999, 2000). Such facilitation occurs for short inter-stimuli intervals and specific combinations of whisker stimuli, and could therefore serve as a detection mechanism for coincidences of behaviorally relevant multi-whisker input.

We have extended these results by demonstrating that pairwise whisker interactions are reshaped when delivering stimulations at a frequency corresponding to behaviorally active states, that is, the frequency of exploratory whisking (Ego-Stengel et al., 2005). Paired whisker stimuli delivered at 8 Hz, where rapid sensory adaptation is engaged, indeed favored supralinear responses. Moreover we found that the facilitation was enhanced when the adjacent whisker was located anterior or dorsal to the principal whisker (Figure 4E, Ego-Stengel et al., 2005). This observation that adaptation tends to facilitate multi-whisker integration has been subsequently confirmed and demonstrated functionally by more recent studies (Higley and Contreras, 2007; Ollerenshaw et al., 2014), suggesting that specific spatiotemporal patterns of two-whisker deflections can be detected by subsets of neurons.

Overall, these results reveal that nonlinear processing is carried out by barrel cortex neurons even with stimulation sequences involving simple pulse-like deflections of only one or two whiskers at a time. Nonetheless, single whisker deflections are seldom encountered in a natural settings and more complex sensory context strongly influences the spatiotemporal

dynamics of cortical responses in the barrel cortex.

2.3: Impact of the sensory context on the linear receptive field properties

We refer here as sensory context to the collection of tactile stimuli taking place in an extended window in time and space, and which can modulate the responses of a neuron to the stimuli present in the center of the receptive field.

Similarly to the visual system (Fournier et al. 2011), increasing the spatiotemporal density of tactile inputs to ranges that are more relevant behaviorally has been shown to affect the integrative properties of barrel cortex neurons. Maravall and collaborators have shown that in the barrel cortex, changes in stimulus statistics induced strong spike rate adaptation (Figure 5A, Maravall et al., 2007) and a corresponding change in the coding space used by the neurons. To do so they applied continuously changing, randomized deflections to several whiskers, and they switched back and forth between two set values of Gaussian variance in position and velocity. Spike-triggered covariance analysis of single units revealed that adapting neurons rescaled their input-output tuning function according to the stimulus distribution. By means of such adaptive gain rescaling, the information transmission about stimulus features was maintained despite the change in sensory context. This feature of neuronal integration in the barrel cortex might be essential to enhance stimulus discriminability across behavioral contexts.

Increasing the dimensionality of the stimulus space can thus help revealing important principles of neuronal processing. In this line of research, Ramirez and collaborators (2014) used a nine-whisker multi-directional stimulator to compare the barrel cortex activity during sparse, non-overlapping stimuli ("simple") versus dense ("complex"), overlapping random stimulations of 9 whiskers in 8 directions (Figure 5B,C). Reverse correlation analysis of the neurons membrane potential was used to identify the spatiotemporal receptive fields obtained in the two conditions. The complex stimulation protocol revealed markedly sharpened receptive fields compared to the ones obtained with sparse whisker stimulation. For example, layer 5 thick-tufted pyramidal neurons, which responded equally to most

whiskers when mapped with conventional single whisker stimuli, became highly focused on the principal whisker during complex stimuli. This switch in coding, most likely due to adaptation mechanisms, is particularly marked in layer 5 neurons. Once again, the sensory context and the level of adaptation (both being highly modulated in natural conditions of whisker tactile explorations) appear to strongly impact the integration of tactile inputs. This stresses the importance of exploring a stimulus space with high dimensionality to obtain a more comprehensive description of cortical input/output relationships.

3. Coding beyond multiple single-whisker stimulations

The nonlinearity of the response to combinations of deflections of two whiskers indicates that beyond the shape of the linear receptive field, spatial features of the tactile stimuli are indeed coded in the barrel cortex in the form of higher order interactions between whisker stimulations.

This nonlinearity results in a major experimental difficulty as there is no simple way to estimate the meaningful spatial features of the whisker stimulation scenes that are extracted by the barrel cortex neurons. This is in contrast to the ON and OFF subfields that can be identified during simple receptive field mappings in the cat V1 cortical area and which are structured in the shape of a Gabor filter (Marcelja, 1980). In addition, the lack of a direct equivalent of the whisker system in humans (although relationship with the human hand touch system have been drawn, Ahissar and Assa, 2016) limits the possibility of an introspection strategy that may provide an experimenter with critical insight in the sensory system (as well as a substantial bias). Overall, very few cues are available to guide a neurophysiologist in the identification of relevant spatial features of multi-whisker stimulations.

To explore this question nonetheless, one strategy has been to start from the observation, already reviewed above, that changes in the sensory context of whisker stimulations can have a strong impact on the barrel cortex functional responses. The so called “context” was initially a change in the density of whisker stimulations outside of the receptive field of the

neurons (Brumberg et al., 1996; Ramirez et al., 2014). But this concept could be extended to whiskerpad-wide homogeneous changes in cross-whisker correlation patterns, thereby defining a spatial structure in statistical terms. This hypothesis was tested by comparing the functional responses obtained during independent dense white noise stimulation on 24 whiskers (in which each whisker receives a different input), versus a correlated dense noise stimulation in which the same deflection is applied to all 24 whiskers simultaneously. Both inputs share the same stimulus density, but one is uncorrelated and the other fully correlated. In this study, we described two separate populations of neurons, one triggered specifically by the correlated stimulus, while a second population of neurons is mostly responsive during uncorrelated stimulations (Estebanez et al., 2012, 2016). Interestingly, these two populations of neurons are spatially segregated in the superficial layers of the cortex, which suggests that they may be part of separate processing circuits and/or project to separate downstream areas (Estebanez et al., 2016).

Beyond whisker pad-wide homogeneous stimulus statistics, whiskers are often subject to heterogeneous touch scenes where dynamic subsets of whiskers contact a surface (Hobbs et al., 2016). These changes in the configuration of stimulated whiskers may be coded by barrel cortex neurons. Again, based on current knowledge, it is difficult to come up with spatial motifs of whisker stimulations that would be relevant to the whisker system. Based on a simple physical intuition of the contact on an object, researchers have hypothesized that the sweeping of a deflection front edge across the whisker pad is a relevant stimulus feature for barrel cortex neurons, similar to the coding by V1 neurons of oriented edges in visual scenes.

To test this hypothesis, ad-hoc whisker stimulation devices have been developed, including a rolling drum holding an actual bar stimulus (Benison et al., 2006) and a stimulator that can deflect columns of whiskers separately (Drew and Feldman, 2007). Using these devices, extracellular recordings of single units (Drew and Feldman, 2007) as well as evoked field potentials (Benison et al., 2006) showed that after a strong increase in activity to the first stimulated whiskers, the functional response is strongly suppressed during the rest of the sweeping stimulus (Figure 6A). This strong suppression is likely to be related to the sublinear summation during the simultaneous stimulation of large counts of whiskers (Chen-Bee et al.,

2012; Hirata and Castro-Alamancos, 2008).

However, the exploration of the parameter space of the bar stimulus using a more generic multi-whisker stimulator (Jacob et al., 2010) shows that emergent parameters of the bar stimulus are actually coded in the whisker system (Jacob et al., 2008). In particular, barrel cortex neurons appear to be sharply tuned to the direction of the movement of the bar stimulus, independently of the direction of the deflection of the individual whiskers (Figure 6B).

More recently, the study of the coding of bar-like stimulus has been extended to awake behaving mice. In a head-fixed behavioral task, barrel cortex neurons turned out to be tuned for the rostro-caudal position of a pole that was advanced along the whisker array (Pluta et al., 2017). Interestingly, neurons coding for different pole positions are organized following a smooth map at the surface of the cortex. This further suggests that bar-like stimuli may be – like in the visual cortex – a key building block of the barrel cortex functional responses to complex tactile scenes.

Similarly, another hypothesis inspired from previous findings in the visual system, particularly in the thalamus, is that the organization of spatial receptive fields follows a center-surround structure. Applying contrasting whisker deflections between the principal whisker and 23 surrounding whiskers revealed a strong enhancement of the response in a subset of barrel cortex neurons, thereby suggesting that these neurons are detectors of local whisker contrasts (Estebanez et al., 2012; Figure 6C).

4. Conclusion

Increasingly, the functional properties identified in the rodent barrel cortex can be compared to the ability of the primary visual cortex of cats and monkeys to capture spatial features in a complex visual scene. Not only do barrel cortex neurons carry low level feature selectivities including whisker direction and phase sensitivity, but also higher order multi-whisker selectivities including center-surround and edge detection. However, in stark

contrast with the primary visual cortex, there is currently no overarching model of the barrel cortex spatial feature selectivity, in part because the description of the barrel cortex spatial tuning features remains incomplete.

To move towards a more complete model of the representations of tactile scenes in the barrel cortex, the combination of several experimental approaches will be required, including the observation of spontaneous and operantly-conditioned rodent behavior, the comparison of the functional properties across whisker-specialist mammal species (Anjum et al., 2006; Dehnhardt et al., 1998), awake behaving studies of the whisker system sensorimotor loop (Jadhav et al., 2009), but also the more classical anesthetized rodent preparation which is the backbone of most of the findings reported in this review. Anesthesia has a clear impact on the functional properties of neurons in the whisker system (Friedberg et al. 1999, Malina et al. 2016, Simons et al. 1992) and alternatives have been proposed including the transection of the facial nerves (Sachidhanandam et al., 2013), but they have not yet been fully characterized and come with their unique drawbacks. We therefore argue that so far, the anesthetized rodent preparation remains the most tractable model available to explore complex multi-whisker feature integration in the rodent barrel cortex.

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FIGURE CAPTIONS

Figure 1. Response properties of barrel cortex neurons to movement features of the principal whisker

A, Direction selectivity in a layer 4 neuron recorded intracellularly in an anesthetized rat, while its principal whisker was deflected in eight different directions. The membrane potential and spike histograms are shown for 8 trials for each direction (PD: preferred direction, OD: opposite direction). The average responses are plotted in polar coordinates, revealing a significant directionality, larger for the spike output than for the synaptic response (from Wilent and Contreras, 2005).

B, Spiking response to slip-stick events in a barrel cortex neuron recorded in the awake rat. Top, Example of whisker motion on a coarse sandpaper (left, position; right, acceleration) revealing a high-acceleration slip event. Bottom, Time course of the response as a function of peak whisker acceleration, revealing strong tuning of the neuron to the slip events (from Jadhav et al., 2009).

C, Neuronal filters revealed by probing rat barrel cortex neurons with white noise as the input (C1). Spike-triggered covariance analysis for this neuron reveals the recurrence of a specific deflection profile on whisker B2 before each spike (C2). Population principal component analysis (PCA) showed that neuronal filters are surprisingly similar, and can be described as linear combinations of two generic filters (red and blue traces, C3) (from Estebanez et al., 2012).

Figure 2. Spatial extent of barrel cortex receptive fields tested with single-whisker stimuli

A, Receptive field of a neuron recorded in layer 4 of the C2 barrel in an anesthetized rat. Left, multi-whisker stimulator controlling independently 24 whiskers. Middle, peri-stimulus time histograms of spikes recorded during sparse noise stimulation (deflection of one whisker every 50 ms; s.a.: spontaneous activity). Right, surprise value (a significance measure) for the response to each whisker (from Le Cam et al., 2011).

B, Subthreshold receptive field of a neuron recorded intracellularly in layer 3 of the C1 barrel in an anesthetized rat (C1 whisker in red). Top, averaged membrane potential in response to the deflection of the C1 whisker (principal whisker, red), C2 (orange), C3 (yellow) and C4 whisker (green). Bottom, microphotograph of the same pyramidal neuron filled with biocytin (Erchova et al., 2006).

C, Cortical spread of spiking activity in response to a single-whisker deflection. Left, 10x10 electrode array placement relative to the barrel map. Middle, peri-stimulus time histograms of spikes recorded during stimulation of whisker C1 in an anesthetized rat. Significant responses are indicated by the red line. Right, Response map in average number of spikes per trial (from Petersen and Diamond, 2000).

D, Subthreshold spread of cortical activity in response to single whisker deflections. Left, schematic and picture of the field imaged over the barrel cortex on the anesthetized mouse brain, while individual whiskers C2 and E4 are successively deflected on the contralateral side. Right, Three snapshots of the Voltage-Sensitive Dye signal, 8, 16 and 24 ms after a deflection of C2 (top) and E4 (bottom) whiskers, showing a spreading wave of activity starting in the appropriate whisker column and invading progressively the whole imaged area (from Ferezou et al., unpublished data).

Figure 3. Multi-whisker stimulation devices to generate complex multi-whisker tactile scenes.

A, The first documented rat multi-whisker stimulation system addressing most macrovibrissae (with 16 independent actuators) was based on solenoids pulling whiskers through stainless steel wirings (from Krupa et al., 2001).

B, The first rat multi-whisker stimulator based on piezoelectric multidirectional actuators allowed the application of controlled deflections to 9 whiskers within the rostro-caudal/ventro-dorsal plane (from Andermann and Moore, 2006).

C, Dense, 24-whisker multidirectional stimulations can be efficiently applied on the mouse whisker-pad (VSD imaging experiment in the anesthetized mouse, from Ferezou, Vilarchao and Shulz, unpublished).

Figure 4. Nonlinear processing of successive stimulations

A, Rapid adaptation of whisker responses. Top: simultaneous extracellular multiunit recordings from the rat thalamus (VPM, upper trace) and barrel cortex (CTX, 390 μm depth, middle trace) during 4 Hz stimulation of the principal whisker (B1). Bottom: Responses of a cortical neuron in the C1 barrel (470 μm depth) to a 4 Hz stimulation of the principal whisker (single trial). Multiple repetitions ($n = 12$) of the first four and the last onset responses in the train are shown below at expanded time scale (from Chung et al., 2002).

B, The subthreshold receptive field shrinks during adaptation. Average response of a layer 4 cell to repetitive stimulation at 18 Hz of nine different whiskers (top left,) in an anesthetized rat. Note that the response to the PW (D2) shows less adaptation than that of the other whiskers. Histograms show the receptive field of the same cell constructed from the peak amplitude of the first, second and third responses to a train of stimuli (from Katz et al., 2006).

C, Adaptation spatially constrains the cortical response. Top: the cortical responses to a single-whisker stimulation in the absence of preceding stimuli. Whisker 1 (W1) and whisker 2 (W2) were adjacent to each other on the rat snout and stimulated separately. Images were averaged over 50 trials. The black ellipses on the images are half-height contours of the two-dimensional Gaussian fits to the images. On the right is the superposition of the Gaussian contours. Bottom: In contrast, when a 10 Hz adapting stimulus was preceding the whisker stimulation, the cortical response was significantly reduced in magnitude and in area (from Ollerenshaw et al., 2014).

D, Facilitation of response for specific two-whisker stimulation patterns. PSTHs of activity of a layer 2/3 neuron for deflections of E1 (principal whisker), E2 (an adjacent whisker), and simultaneous or successive deflections of E1 and E2 in an anesthetized rat. The latency difference of stimulation of individual whiskers was 3ms. Note that response facilitation peaked when E2 stimulation preceded E1 stimulation by a few milliseconds, when evoked potentials are expected to coincide in the cell (from Shimegi et al., 1999).

E, Facilitatory and suppressive interactions depend on the frequency of stimulation. Left:

mean facilitation index (condition-test ratio, CTR) as a function of interstimulus intervals (ISI) averaged for all tests at 8 Hz (white symbols) and 0.5 Hz (black symbols) (86 and 42 multi-units, respectively). Note that sublinear and supralinear summations resulted in ratios <1 and >1 , respectively. Middle graphs: The percentage of cases for which a significant facilitatory (white bars) or suppressive (black bars) effect was found as a function of ISI (1 neuron may contribute multiple times to the histogram) are depicted for whisker stimulation at 8 Hz and 0.5 Hz. Right: Average percentages depicted as polar plots, as a function of the location of the adjacent whisker relative to the principal whisker on the rat snout (from Ego-Stengel et al., 2005).

Figure 5. Impact of tactile input density on neuronal dynamics in the barrel cortex

A, Adaptive responses to switching variance of noise stimuli. The principal whisker together with its adjacent whiskers were deflected in one dimension with a random sequence of positions in an anesthetized rat. Instantaneous positions were distributed according to a Gaussian distribution whose variance was switched every 5 s. Top left: Absolute spike rate of a single unit averaged over switching cycles (1 080 repetitions, bin size, 100 ms). Below is normalized rate modulation. Top right: rate modulation pooled over all adapting single neurons ($n = 9$, average $\pm$ standard deviation). Rate modulation was robust and occurred over a similar timescale across the population. Bottom right: adaptation ratios. The firing rate at steady state (binned 4–5 s after each upwards switch in stimulus variance) was divided by the rate immediately after switching to high variance (binned 0–100 ms after the switch). Left: data points. Filled gray square, non-adapting neuron ($n = 1$); filled black circles, adapting single neurons ($n = 13$); open circles, adapting multi-neuron clusters ($n = 20$). Right: histogram of adaptation ratios for all recordings shown on the left side. Only a single cortical neuron showed non-adapting behavior. The asterisk denotes that this neuron's adaptation ratio was significantly different from that of the rest of the population ($p = 0.001$) (from Maravall et al., 2007).

B, Spatiotemporal receptive fields of barrel cortex neurons revealed by reverse correlation of synaptic inputs. Left, schematic of the experimental setup. Rat barrel cortex neurons were recorded intracellularly during simple or complex stimulation of nine whiskers (W1 to W9) delivered by means of multi-directional piezoelectric stimulators. Simple stimulations consisted in the ramp-and-hold deflection of one whisker selected randomly among the nine, and moved in one of the eight cardinal directions every 1.5 s while other whiskers did not move. The complex stimulation protocol where the nine whiskers are moved simultaneously and continuously is illustrated. Each arrow represents an independent deflection of one whisker. Deflections occurred stochastically in time (frequency of ~ 9.1 Hz) and direction (among 8 possible, C: caudal, R: rostral, D: dorsal, V: ventral). Nonlinear stimulus representation where whisker movements are represented in an eight angle-binned space instead of Cartesian space is shown on the right panel (from Ramirez et al.,

2014).

C, Complex stimuli reveal markedly sharpened receptive fields relative to conventional stimuli. Population-averaged spatiotemporal receptive fields were calculated for neurons of the same cell type based on complex multi-whisker stimuli (left) or simple single-whisker stimuli (right) (from Ramirez et al., 2014).

Figure 6. Coding a spatially structured multi-whisker features

A, Recording of a neuron in the D2 column of the barrel cortex during a sweeping bar stimulus across the whiskerpad, starting from the Straddlers arc (red), arc 1 (green) or arc 2 (blue), in an anesthetized rat (PW: principal whisker). Responses to whiskers stimulated downstream from the stimulus onset location are suppressed (adapted from Drew and Feldman, 2007).

B1, Bar stimulus sweeping the whisker pad in one of eight directions. Note that although the bar is advancing in an oblique direction, the local whisker deflections are backward. B2, Receptive field of a neuron centered on C2 in the rat barrel cortex. B3, Tuning of the same neuron to the direction of the bar sweeping movement (C: caudal, D: dorsal, R: rostral, V: ventral), (from Jacob et al., 2008).

C1, White noise applied to the principal whisker (red) and 23 adjacent whiskers at the periphery (black), in an anesthetized rat. C2, Interaction between the principal and adjacent whiskers in the phase space (see Figure 2C3) showing that anti-phased stimuli (blue line) are optimal for this neuron. C3, Population analysis of the optimal phase relationship between principal whisker and surround, showing that in most neurons with responses enhanced by out of phase surround stimuli, antiphased stimuli are optimal (adapted from Estebanez et al., 2012).

Representation of tactile scenes in the rodent barrel cortex

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Highlights

- Barrel cortex neurons respond to a wide repertoire of whisker movement features.
- Neurons in the barrel cortex code also for high order multi-whisker information
- A general model of the representation of multiwhisker information in the barrel cortex is still missing

