# Introduction

Our recent sensations affect current perception of the environment. The neural correlates of this process are loosely termed adaptation. The ubiquity of adaptation suggests that it has considerable advantages, possibly serving similar functions across different sensory modalities. Sensory adaptation founds at all levels of sensory systems processing, from the receptors to the highest stages of processing. Adaptation enhances information transfer (Barlow, 1961) by emphasizing changes in intensity rather than absolute values and by adjustment of neuronal gain response, increasing it when background inputs are weak and reduce it at high intensity of sensory inputs.

Adaptation in the vibrissa system of rodents has been studied for many years, revealing its prominent effects on neuronal response at different stages of sensory processing. Rodents are nocturnal animals and often live in burrows and other habitats of complete darkness where the only modality that enables them to gather *instantaneous* information on the physical structure of their environment is the somatosensory system and in particular the vibrissa system. To do so rodents sweep their whiskers back and forth against objects at narrow range of frequencies, between 5 to 25 Hz in short bouts of up to a few seconds each time (Berg and Kleinfeld, 2003) (Voigts et al., 2008).

Mechanical information is transduced into spikes in axons that innervate the whisker's follicles. These action potentials are transmitted via trigeminal ganglionic axons to the central nervous system (CNS) very rapidly. The adaptation properties of ganglion cells were studied based on their response properties in the first few milliseconds after ramping the position of the whisker and holding it in a new position. This stimulation approach revealed two major populations of cells; slowly adapting (SA) cells, which have Ruffini endings or contact Merkel cells (Wellnitz et al., 2010) and rapidly adapting (RA) cells, engulfing the follicle with lanceolate endings (Zucker and Welker, 1969; Shoykhet et al., 2000; Lottem and Azouz, 2011). However, in this review we focus on slower time scales of adaptation and mostly discuss the adaptation properties of somatosensory neurons within the CNS, starting in the brainstem tactile circuits to the somatosensory cortex via the thalamus. Different methods and paradigms of stimulation were used to study adaptation in this system. However, the most common approach has being stimulating the whiskers by puffing air or attaching mechanical actuators to a single whisker or several whiskers and apply a train of punctuated or sinusoidal stimuli at different frequencies or intensities. Other studies explored the adaptation properties in this system using continues noise stimulation. Despite differences in the way whiskers are stimulated several principles emerged from these studies. In particular, we will focus on subthreshold responses of neurons as they helped in revealing some of the underlying mechanisms of sensory adaptation in the somatosensory system.

# Adaptation depends on the frequency of vibrissa stimulation

Increasing the frequency of whisker stimulation entails greater adaptation in the somatosensory system. This was observed in first order trigeminal ganglion (Fraser et al., 2006), the trigeminal complex (Ganmor et al., 2010; Mohar et al., 2013), thalamus (Khatri et al., 2004) (Hartings et al., 2003) and in the barrel cortex (Ahissar et al., 2000) (Heiss et al., 2008; Khatri et al., 2009). Importantly, adaptation is strongly affected by the intensity of stimulation (Ganmor et al., 2010; Mohar et al., 2013), the shape of each stimulus (Fraser et al., 2006) (Khatri et al., 2004) or by animal’s brain-state or depth of anesthesia (Castro-Alamancos, 2004; Katz et al., 2012). Another important parameter which is sometimes overlooked is the recording location as different cortical layers have specific adaptation properties (Sosnik et al., 2001a) and this specialization is prevalent in L4 where barrel and septal neuron exhibit different response properties (Chakrabarti and Alloway, 2009). Hence, direct comparison of the degree of adaptation across studies which used different experimental parameters may show different results. Yet, in all studies greater adaptation was observed with increasing the frequency of stimulation. When identical whisker stimulation was used to compare the degree of adaptation across different stages of processing, a greater adaptation was reported in downstream neurons (Sosnik et al., 2001a, 2001b; Ganmor et al., 2010) (Khatri et al., 2009) . For example, neurons in the principal nucleus of the trigeminal complex (PrV) adapt more when compared to neurons in the trigeminal ganglion, but they exhibited less adaptation compared to the cells that they target, in the ventral posteromedial nucleus of the thalamus (Ganmor et al., 2010, I will cut and paste from his paper to show it!, find papers of Ahissar with the puff and maybe more). A similar picture emerged in studies of adaptation of thalamic and cortical cells (Sosnik et al., 2001a; Khatri et al., 2004).

Add differences in layers, intensity, angle, passive/active

# Possible role of short term synaptic plasticity in tactile adaptation

Short term synaptic depression (STD) is believed to play a pivotal role in tactile adaptation in the somatosensory system. However, a gradual reduction in firing response during train stimulation could result, in theory, also from a slow buildup of inhibition (Staley and Mody, 1992; Borg-Graham et al., 1998) (Dealy and Tolhurst, 1974) or by activating hyperpolarizing intrinsic conductances (Sanchez-Vives et al., 2000) (Carandini and Ferster, 1997). In-vivo intracellular recording studies demonstrated, however, that during train-stimulation of the whisker the evoked synaptic response becomes progressively smaller from one stimulus to the next, strongly suggesting that STD (short term depression) plays crucial role in tactile adaptation. Gradual reduction in synaptic response during tactile adaptation was reported for cortical cells (Heiss et al., 2008) (Cohen-Kashi Malina et al., 2013) (Higley and Contreras, 2006), thalamic neurons (Deschênes et al., 2003) and for neurons in the trigeminal complex (Mohar et al., 2013). Since thalamic cells exhibit weaker adaptation compared to cortical cells, the stronger reduction of cortical response during repetitive stimulation supported the hypothesis that STD of thalamo-cortical and intracortical synapses is involved in cortical adaptation. Intracellular recordings of cortical cells in thalamo-cortical brain slices, where thalamic and intracortical inputs were independently stimulated suggested that adaptation in the cortex mostly results from depression of thalamo-cortical synapses rather than depression of intracortical synapses (Gabernet et al., 2005) (Gil et al., 1999). This conjuncture was validated by Chung and her colleagues (2002) as they showed, by testing the effect of adaptation on cortical response to electrical stimulation of thalamo-cortical and cortico-cortico pathways, that tactile adaptation of layer 4 cells results from STD of thalamo-cortical synapses rather than of intracortical connections. In contrast, intracortical unitary excitatory synaptic potentials in layer 4 and upper layers of the somatosensory cortex exhibit profound STD, suggesting that tactile adaptation results from depression of local recurrent connections (Petersen, 2002) (Cowan and Stricker, 2004) (Beck et al., 2005) .

# Cascading adaptation in the somatosensory system and iceberg effect.

To establish a direct link between tactile adaptation and STD, one need to show that individual unitary connections depress during this process by recording simultaneously presynaptic firing and postsynaptic membrane potential in connected cells. However, due to threshold of action potentials, adaptation may be augmented in downstream neurons even if no mechanisms of adaptation exist locally, including intrinsic or short-term synaptic plasticity. To illustrate it we simulated a feedforward network in which afferents from 45 neurons converged onto a single cell. In the first case (Fig. 1), we assumed that the adaptation of a downstream neuron (‘Integrating neuron’) is purely inherited from its adapting inputs. For these inputs adaptation was simulated as a gradual reduction in their firing probability during train stimulation. Since we did not include any local mechanism of adaptation for the integrating neuron, each unitary post synaptic potential (uEPSP) remained unaffected during the repetitive stimulation train, adaptation, therefore, results from a gradual reduction in the number of inputs that are summed for each subsequent stimulus. In the second case, the firing probability of the upstream cells was kept constant during the train, but STD was simulated for their synaptic contacts of the integrating neuron. Importantly, the two proposed schemes exhibit similar adaptation patterns. Clearly, these two proposed schemes are not mutually exclusive and others network mechanisms, such as feedback connections were not included. Moreover, the upper panels show that due to threshold effect (‘iceberg effect’) the post synaptic cell may exhibit more adaptation than its inputs. Weaker adaptation in downstream neurons is yet possible, for example, if these cells exhibit a low threshold and saturation of their subthreshold response for weak input. In summary, adaptation at a given stage of processing may cascade or inherited from earlier stages of sensory processing and can be augmented due to spike threshold.

# The specificity of adaptation in the vibrissa system

Adaptation is said to be specific if the response to a given stimulus is not affected by adapting the cell by a different stimulus. In the auditory cortex, for example, the specificity of adaptation was mostly studied in the context of sound frequency (Ulanovsky et al., 2004) (Reches and Gutfreund, 2008). Whether or not adaptation is specific to a particular feature can provide important information both on the mechanisms of adaptation and on the network organization of sensory afferents. Non-specific adaptation may reflect intrinsic mechanisms, such as voltage dependent potassium currents (Carandini and Ferster, 1997) (Sanchez-Vives et al., 2000) or buildup of global inhibition (Staley and Mody, 1992; Borg-Graham et al., 1998) . However, it can also cascade from an earlier stage, where the non-specificity is induced by intrinsic mechanisms at the earlier stage or due to STD of converged afferents of the earlier stage. Importantly, specific adaptation strongly suggests that adaptation is not caused by intrinsic mechanisms in the recorded cell (Katz et al. 2006////XX). It is important to emphasize that specific adaptation does not indicate necessarily that inputs that encode different type of information converged onto the recorded cell. For example, inputs may adapt independently at separated pathways, converged and later cascade to the recorded cell without further augmentation of adaptation.

Several studies of the barrel cortex examined the specificity of whisker adaptation to different features such as whisker identity, stimulation intensity and the direction of whisker deflection. The specificity of adaptation to whisker identity in the barrel cortex of anesthetized rats was examined intracellularly by Katz et al. (2006). In this study they found that the response of neurons in layer 2/3 and 4 to a given whisker was not affected if it was delivered following repetitive stimulation of a neighboring whisker to which cells responded (Fig. 2), indicating that adaptation to whisker identity was highly specific. The prominent specificity of adaptation implies that intrinsic mechanisms for adaptation were absent in the recorded cells. These results also suggested that L4 cells are mainly innervated by single whisker thalamic afferents, in agreement with anatomical and electrophysiological studies (Agmon et al., 1995; Keller and Carlson, 1999) (Land et al., 1995). However, a recent study, in which an oddball paradigm was used, shows that the specificity of adaptation to whisker identity in layer 4 is significantly smaller compared to upper and lower cortical layers (Musall et al., 2015). The discrepancy between these two studies may reflect differences in experimental conditions such as the depth and type of anesthesia and simulation intensity. The receptive field size of brainstem and thalamic neurons is strongly modulated by the depth of anesthesia; increasing the depth of anesthesia profoundly reduces the number of whiskers that upon stimulation evoke a response in these neurons (Friedberg et al., 1999) (Katz et al., 2012). This discrepancy may also stem from differences in the pattern and strength of stimulation, known to affect the degree and pattern of tactile adaptation at brainstem and thalamic cells (Mohar et al., 2013, Ganmor et al., 2010).

The specificity of adaptation to other features of stimulation, such as the velocity and direction of whisker deflection was studied using extracellular recordings of single units. The effect of adaptation on the angular tuning of cortical cells to the direction of whisker deflection was studied by Khatri and Simons (2009). In this study they demonstrated that adaptation reduced the response of cortical cells to any direction regardless the direction of the adapting stimulation, suggesting that the specificity of adaptation to this feature in the cortex is weak. The specificity of adaptation to the direction of whisker deflection was also studied by Musall et al. (2015) where oddball paradigm was used to examine the specificity to caudal and rostral whisker deflections. In agreement to the earlier study, they found that the specificity of adaptation to the direction of whisker deflection was weak, although significant. The same study also investigated the specificity of adaptation to the velocity and similar to the specificity of adaptation to the direction of whisker deflection, its specificity to the velocity was weak but significant.

# Intensity dependent adaptation and coding of stimulus intensity in the somatosensory system

Studies of STD led to highly successful mathematical descriptions of this phenomenon (Tsodyks and Markram 1997). Assuming that tactile adaptation results mostly from STD gives rise to several interesting predictions. One of these predicts that increasing the intensity of stimulation, which is followed by higher presynaptic firing probability, will result with greater depression during sustained sensory stimulation due to depletion of synaptic resources and the relatively slower recovery processes (Ganmor et al., 2010, Fig. 3B). This prediction was tested in the lemniscal pathway of the somatosensory system. In contrast to this prediction, increasing the amplitude and velocity of whisker deflection entailed less adaptation of evoked excitatory inputs of layer 4 cells of the barrel cortex (Ganmor et al., 2010, Fig. 3A). Through a series of recordings along the entire lemniscal pathway as well as from first order ganglion cells, this study showed that the source for this unexpected form of adaptation lies in PrV neurons of the trigeminal complex (Fig. 3E). The authors of this study suggested that such peculiar form of adaptation may act to counterbalance the effect of STD during sustained stimulation and by that to increase the duration and impact of persistent and perhaps relevant sensory inputs that otherwise would depress quickly.

In another study (Mohar et al., 2013), the results of Ganmor et al. (2010) were confirmed using intracellular recordings of PrV neurons, demonstrating that this peculiar form of adaptation already exists at the synaptic level. Surprisingly, while searching for PrV cells, they recorded also from SpVi cells, which form the starting point of the paralemniscal pathway, and found that increasing the intensity of stimulation entailed greater adaptation in these cells, as expected from STD models (Fig. 3F). Moreover, this study showed that increasing the intensity of stimulation of adjacent whiskers of PrV cells results with similar adaptation pattern that was recorded in the SpVI, namely as expected from STD models. Although the mechanisms of PrV adaptation are unknown, Mohar et al. (2013) suggested that it may result from intersubnuclear inhibitory projections from SpVi to the PrV (Furuta et al., 2008); as the intensity of stimulation increases, inhibitory neurons of the SpVi adapt more, a process that leads to greater disinhibition of PrV cells and consequently to a decrease in the rate of adaptation. This possibility, however, remains unknown since it is unclear if inhibitory neurons in SpVi adapts as expected from STD models.

These findings raised the possibility that the ability of neurons belonging to these two nuclei to encode the intensity of stimulation under adaptation depends on the intensity context of stimulation. Indeed, Mohar and his colleagues (2015) found that although the two nuclei encode non-adapted stimuli in a very similar manner, adaptation introduces distinct differences in their coding behavior. Under adaptation, PrV neurons, at the starting point of the lemniscal pathway, better encode the fluctuations in stimulus intensity when their intensity is high, whereas neurons in the SpVi, the origin of the paralemniscal pathway, encode the fluctuations during episodes of weak tactile stimulation (Fig. 3). Importantly, these differences were already observed at the level of the subthreshold synaptic potentials. Hence, adaptation smooths the intensity-response curve of PrV when the intensity of stimuli is high and smooths the response curve of SpVi cells for weak stimuli.

What could be the functional role of these distinct adaptation patterns in early stages of tactile processing? Mohar et al. (2015) suggested that the output of SpVi cells might be more relevant for perception in discrimination tasks, extracting subtle details under low intensity palpation, whereas the output of PrV cells is used during high intensity detection tasks. Future studies may test this hypothesis in behaving rodents.

The relations of the above studies regarding intensity dependent adaptation and studies describing the role of adaptation in detection and discrimination of stimulation intensity of cortical cells are not clear. Adaptation of cortical cells in the barrel cortex improves the discriminability of sensory inputs by smoothing the response curves of neurons to different intensities (Wang et al., 2010; Adibi et al., 2013; Ollerenshaw et al., 2014). Yet, the mechanisms that improve coding under adaptation are not fully understood. Improved coding of cortical cells under adaptation may reflect early processing in upstream neurons of the brainstem trigeminal complex (Mohar et al., 2015). Conversely, other studies showed that enhanced coding of stimulus intensity of cortical cells does not mirror thalamic cells as adaptation poorly changes their intensity-response curves (wang et al., 2010). Rather, Wang and his colleagues (2010) suggested that adaptation reduces the degree of synchrony in the thalamus, a process that is transformed into intensity dependent graded response in cortical cells and by that improves coding under adaptation. Clearly, more research is required to reveal the underlying mechanisms that improve coding of tactile stimulation under adaptation.

# Adaptation and the balanc­e excitation and inhibition in the cortex

Despite of constituting a minority, inhibitory interneurons in the cortex are vastly more diverse than excitatory cells with respect to their axonal and dendritic arborization patterns (Ramon Y. Cajal, 1911; Jones, 1975). Histochemical and morphological methods revealed that GABAergic neurons in the cortex are subdivided into at least 4, almost non-overlapping, classes: Parvalbumin (PV), somatostatin (Sst), and 5-HT3aR-positive neurons composed from vasoactive intestinal peptide (VIP) and neurogliaform (NGF) expressing cells which together with principle cells form complex circuits (Kawaguchi and Kubota, 1997; for a review see Harris and Mrsic-Flogel, 2013). Anatomical and electrophysiological studies suggest that these classes have different roles in sensory adaptation, mostly due to the diverse facilitating/depressing properties of their inputs and outputs. For example, whereas excitatory inputs of PV cells are mostly depressed, those of Sst show substantial facilitation (Silberberg and Markram, 2007; Pala and Petersen, 2015). Importantly, during whisking, different classes of interneurons exhibit different activities; 5HT-expressing GABAergic neurons (VIP and NGF) increase their firing rate, whereas the firing rate of Sst neurons is reduced (Gentet et al., 2012). However, the role of different classes of cortical interneurons in tactile adaptation is yet to be studied.

At cortical layer 4, thalamocortical afferents are subjected to a major transformation; they synapse onto excitatory neurons but also onto local inhibitory neurons which in turn inhibit both excitatory cells and other inhibitory cells (Cruikshank et al., 2007) (Trevelyan et al., 2007) (Beierlein et al., 2003) (Agmon and Connors, 1991; Gabernet et al., 2005). Whisker stimulation evokes in cortical cells a raid excitatory response followed almost immediately by a prominent inhibition (Higley and Contreras, 2006; Heiss et al., 2008). The inhibitory response of excitatory cells is likely to result from synaptic inputs that are driven by fast-spiking cells (Beierlein et al., 2003; Gabernet et al., 2005; Cruikshank et al., 2007) (Ji et al., 2016) (Zhou et al., 2014).

It was suggested that feedforward inhibition in principle cells limits the integration time window of excitation and therefore confines the rate and timing of action potentials (Gabernet et al., 2005; Cruikshank et al., 2007). In-vivo intracellular recording studies showed that both excitatory and inhibitory synaptic inputs of cortical cells adapt when whiskers are stimulated repetitively. However, inconsistent results were reported regarding the effect of adaptation on their ratio. According to one study (Higley and Contreras, 2006), the balance between excitation and inhibition is unaffected when cortical cells are adapted during repetitive stimulation of the whiskers. On the other hand, other studies showed that inhibition adapts more and faster than excitation and therefore the balance shifts towards excitation (Fig. 4A-B, Heiss et al., 2008; Cohen-Kashi Malina et al., 2013). This shift in the balance may increase the throughput of information during repetitive stimulation in the face of reduced excitatory drive of cortical inputs, allowing cells to respond and perhaps to preserve neuronal and metabolic resources (Heiss et al., 2008). As inhibitory inputs adapt more than excitatory inputs, the integration time widow of excitation is widened and therefor temporal precision of firing is reduced (Gabernet et al., 2005). Perhaps this explains the reduction in the residual correlation of firing between neurons (i.e., noise correlation,) during adaptation of neurons in the barrel cortex (Khatri et al., 2009; Adibi et al., 2013).

The differential effect of adaptation on excitatory and inhibitory evoked synaptic inputs raised the possibility that these inputs recover differently from adaptation. To test this, Cohen-Kashi Malina (2013) examined the response of layer4 cells to single deflection of the principle whisker at different time intervals following the adapting stimulation. Surprisingly, in a significant subset of cells the response to a single whisker stimulation was facilitated when delivered a few hundred milliseconds after the adapting stimulation (Fig. 4C-D).Intracellular recordings showed that this facilitation was associated with a delayed recovery of inhibition relative to excitation (Fig. 4E-G). Because of a slower recovery of inhibitory inputs, neurons become hypersensitive shortly after the termination of the adapting stimulation and elicited more spikes compared to the non-adapted response. This hypersensitivity may explain why neurons in the barrel cortex respond more vigorously to aperiodic stimulation compared to periodic stimulation (Lak et al., 2008). The increased sensitivity of cortical neurons following adaptation might be related also to the increased human performance in tactile discrimination tasks when a test stimulation is delivered shortly after a repetitive one (Harris et al., 2002). However, a systematic comparison of the adaptation properties of various types of inhibitory neurons such as PV+, SOM + and VIP+ as well as excitatory neurons remains to be determined.

Inhibition and adaptation might share similar functions in regulating activity of cortical circuits and in encoding information. It was suggested that by balancing the excitatory inputs, inhibition prevents rapid recruitment of the entire population and therefore improving the dynamic range of these circuits which eventually enhances their ability to encode relevant information (Isaacson and Scanziani 2011). The output of a single cortical cell diverges onto many other cortical cells. If simultaneous activation of a few input afferents is sufficient to bring a cell to threshold, neuronal activity will spread rapidly to the entire population. However, if in the same circuit excitation is proportionally balanced by inhibition, the number of afferents that can bring a cell to threshold increases and therefore the recruitment of the population is more progressive and graded. When excitation is balanced by inhibition, therefore, the size of the response better represents a wider range of combinations of afferent inputs. Adaptation might improve coding and reduce the explosion of activity in a similar manner to inhibition; by reducing the response of a postsynaptic cell to a given stimulation. This is in particular the case if adaptation results from local, intrinsic or synaptic mechanisms, such as activation of hyperpolarizing currents or synaptic depression. In the latter case, for example, synaptic depression decreases the amplitude of each unitary synaptic input, and therefore a larger number of afferent inputs is required to bring the membrane potential to threshold. As excitatory inputs adapt in the barrel cortex when whiskers are repetitively stimulate, inhibition might not be required anymore to prevent runaway excitation and to encode the intensity of sensory input. Indeed, this may explain why the balance between excitation and inhibition during sensory adaptation is skewed toward excitation (Heiss et al., 2008; Cohen-Kashi Malina et al., 2013). Yet, it is unknown if adaptation indeed increases the number of active input afferents that are required to elicit a firing response when compared to the non-adapted response.

Conclusions

In the somatosensory cortex adaptation is manifested at different stages of processing, from the receptors all the way to the cortex. Different studies indicate that short term synaptic depression is the major mechanism that is responsible for adaptation in this system. Yet, at each stage of processing, adaptation can be inherited from earlier stages. That STD plays pivotal role in adaptation is supported by the high specificity of adaptation to whisker identity or the direction of whisker deflection and the lack of findings that may support other mechanisms such as intrinsic or build-up of inhibition.