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OPINION ARTICLE

The referential brain: why do some neurons learn and some do not? [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Brain is phenomenally plastic and exhibits this capacity well into adulthood. Neuronal plasticity can be studied by using different adaptation protocols. Post-adaptation neurons typically show attractive and repulsive shifts even though challenged by the same adapter. Using orientation columns as a paradigm, we argue and suggest that repulsive shifts are essentially fundamental to preserve the functional organization of the cortex, and thus, maintaining the functional homeostasis of the brain.

Keywords

referential brain , repulsive shifts , attractive shifts , plasticity , visual cortex

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Any reports and responses or comments on the article can be found at the end of the article.

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In daily life we use reference points to evaluate and analyse options around. Brain exhibits phenomenal plasticity during youth and even adulthood that helps animals adapt to different experiences (Bachatene *et al.*, 2015b; Dragoi *et al.*, 2001; Hensch, 2005; Kohn, 2007; Turrigiano & Nelson, 2004).

In general, neurons in the brain are selective to certain features. For example, a primary visual neuron (V1) is selective to a range of orientations (Hubel & Wiesel, 1962; Hubel & Wiesel, 1968; Swindale, 1998). Neuronal plasticity can be studied by employing several techniques and protocols (Kohn, 2007; Turrigiano & Nelson, 2004) such as visual deprivation and adaptation. Adaptation refers to the imposition of a non-optimal stimulus (adapter) within neuronal receptive fields for specific periods of time (usually several minutes) to alter their response behaviour (Kohn, 2007). Indeed, using various techniques in different brain areas, the effects of adaptation have been investigated on various neuronal properties such as orientation selectivity (Bachatene *et al.*, 2015b; Dragoi *et al.*, 2000; Gutnisky & Dragoi, 2008; Ghisovan *et al.*, 2009), motion (Kohn & Movshon, 2003), spatial frequency (Bouchard *et al.*, 2008; Marshansky *et al.*, 2011), and contrast (Baccus & Meister, 2002). After adaptation protocol, neurons typically show two types of behavioural shift patterns: attraction and repulsion. An attractive shift is the displacement of a tuning curve toward the adapter following adaptation, whereas a repulsive shift corresponds to the movement of the tuning curve away from the adapter. Some neurons refract the adapter and do not change their selectivity (Jeyabalaratnam *et al.*, 2013).

Interestingly, contingent upon the duration of stimulus, neurons may predominantly shift in one characteristic fashion. For example, a 3-min adaptation (Dragoi *et al.*, 2000) of visual neurons leads to a majority of repulsive shifts, whereas, a prolonged adaptation (> 6 min) potentiates attractive shifts (Bachatene *et al.*, 2015b; Cattani *et al.*, 2014; Ghisovan *et al.*, 2009). Why do some neurons learn and some do not, even though challenged by the same adapter? Does this apply to all the brain regions?

Here we put forth a concept through our recent results on the functional reprogramming of orientation columns in the visual cortex (Bachatene *et al.*, 2015b). In that report, we showed that neurons at the adapted and non-adapted cortical sites exhibited similar pattern of shifts. It is particularly interesting that the non-adapted neurons (not challenged by the adapter) also displayed changes in their orientation selectivity (they exhibited both types shifts). This is illustrated as an example in Figure 1. The upper row displays a hypothetical layout of orientation columns in control conditions. The activities of nine neurons under observation were recorded simultaneously that were tuned distinctly at each location (neurons at each location are linked by a black triangle; all three sites had non-overlapping receptive fields). After the adaptation procedure, neurons at each site changed their selectivity irrespective of the fact that only neurons tuned to 90° (pre-adaptation, red-columned neurons, middle triangle) were challenged with an adapter (157.5° degree orientation, purple bar). Notably, post-adaptation, two neurons (middle triangle, purple neurons) at the adapted site exhibited an attractive shift whereas one neuron displayed repulsion. In other words, only two neurons learnt the adapter whereas

Figure 1. Functional reconfiguration of orientation columns post-adaptation. The upper row corresponds to the orientation layout of columns in the control (pre-adaptation) condition. The triangles show three distinct groups of neurons (with non-overlapping receptive fields) under observation within different columns. After an adaptation procedure (neurons in the red column, 90°, are adapted to 157.5°), the orientation layout of the columns is reconfigured (lower row). It is to be underlined that, although only neurons corresponding to 90° column were challenged by an adapter, neurons in other columns (non-adapted) also changed their selectivity. Two out of three neurons at the adapted site changed their selectivity toward the adapter, whereas one neuron shifted its selectivity away from the adapter. The repulsive neurons may have an important role to play in maintaining the functional dogma of orientation processing in the visual cortex. Note: Each colored sphere represents a neuron.

the third neuron swayed away from this behaviour. Interestingly, non-adapted neurons in other columns (left and right triangles) also displayed orientation selectivity shifts following adaptation.

Many reports (Bachatene *et al.*, 2013; Jia *et al.*, 2010; Wertz *et al.*, 2015) have shown and suggested that neuronal dendrites contain synapses corresponding to all the orientations. Within this framework, after a prolonged adaptation, the synapses representing the adapter would strengthen and become active, thus giving rise to a novel selectivity for the neuron. Therefore, new local networks are framed potentiating a changed column. Within this dynamic interplay, most local neurons may wire together and shift their responses in conjunction with each other toward the adapter whereas a minority may deflect away (repulsion) to participate in conservation of the columnar dogma. Few neurons may remain

unaffected that are termed refractory neurons. Once this reference is set, other columns would systematically tilt to achieve their ultimate destiny without leaving an orientation hole. Therefore, repulsive neurons have a significantly equal role as attractive neurons to play in organizing principles of functional sensory processing. Biologically, this implies a homeostatic phenomenon allowing a sensory feature to conserve a basic state that will allow further plastic modifications (Bachatene *et al.*, 2015a; Turrigiano & Nelson, 2004). Thus, the cortical column is reframed with an equal representation of each optimal stimulus.

From the above paradigm, it is suggested that the brain, especially the cortex functions on such organizing principles. In fact, similarly to the visual cortex, distinct functional maps are present in other brain regions too. For example, the auditory cortex may also be functionally reorganized in such fashion (Nahum *et al.*, 2013). Although, neurons are arranged in a salt-and-pepper fashion in lower vertebrates, yet they exhibit selectivity to properties and may

also reorganize through similar connectivity principles as higher vertebrates. Therefore, we suggest that neuronal functioning is referential in nature. This eventually facilitates the brain's ability to modify itself easily (plasticity), to form novel networks, and most importantly, to maintain the functional homeostasis.

Author contributions

VB wrote the manuscript. LB helped with critical remarks and manuscript writing. Both authors agreed to the final content of the article.

Competing interests

The authors declare no competing financial interests.

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Stanislaw Glazewski

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Bharmauria and Bachatene propose that the neurones termed “repulsive” (as they change their preferred orientation while challenged with the adaptor but do not follow it) are fundamental “to preserve the functional organisation of the cortex” or as it is found in a different place “to participate in conservation of the columnar dogma”. I neither recognise the arguments for this concept or the evidence that it is based on. Why would the presence of refractory neurones not be sufficient if any “columnar dogma” or “the reference” is required? Additionally, as the preferred orientation of neurones changes with the duration of adaptor presentation, it is plausible that the repulsive and even refractory neurones are still shifting to the adaptor’s orientation. If the shifting is never absolute the remaining refractory and repulsive neurones could just have no function (noise). In any case the eventual function of refractory and repulsive neurones can be at present tested in small-scale experiment, as the appropriate technology is available. On the other hand, it would be much easier to test at first whether the repulsive and refractory neurones really exist (long adapting experiment) and if they are whether they are fixed at these functions (series of different adaptors’ presentation experiment with use of the same population of neurones). The results should aid the concepts, which are premature at present.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Feb 2017

Vishal Bharmauria, Université de Montréal, Montréal, QC, Canada

We thank the reviewer for his comments on the manuscript. The comments of the reviewer have helped in clarification of the manuscript further. We have added a paragraph on the

role of repulsive shifts. In fact, we have suggested this concept based on our recent findings (Bachatene *et al.* 2015b) on the visual cortex of the anaesthetized cat that such a phenomenon maybe occurring after adaptation procedures. We would like to emphasize that in addition to the neurons at the adapted site, neurons at the non-adapted sites also changed their selectivity. In fact, many reports (these papers have been cited in the article) have shown that refractory neurons exist in the cortex, however, refractory neurons and repulsive neurons could even reverse/change their orientation selectivity shift-directions toward the adapter after repetitive adaptations (Ghisovan *et al.* 2008). Indeed, neurons may be fixed at these functions, but only to a certain period of adaptation as they may change their properties as the adapter duration is changed (Ghisovan *et al.* 2008). We have even tested shift amplitudes between 6 min until 24 min (Bachatene *et al.* 2015) of adaptation and the tested neurons always fall into three categories: attractive, repulsive and refractory neurons. However, longer adaptation protocols may potentiate attractive shifts in general. Although, the concept maybe premature at present but if one were to imagine the simultaneously recorded neurons from a column as an ensemble of neurons, the role of refractory neurons could be hypothesized as follows: There is plenty of evidence nowadays that in an ensemble of neurons, some neurons are strongly embedded in the circuits whereas others change their properties due to synaptic changes occurring at their dendrites. Such strongly embedded neurons may be compared to the refractory neurons, whereas others undergo change in their properties through short term plasticity. Indeed, further experiments could be designed to explore the exact roles of refractory neurons in circuits. However, within the framework of the columnar organization, they seem to be important in preserving this functional dogma.

Ghisovan *et al.* 2008. Visual Cells Remember Earlier Applied Target: Plasticity of Orientation Selectivity

Bachatene *et al.* (2015) Summation of connectivity strengths in the visual cortex reveals stability of neuronal microcircuits after plasticity. *BMC Neurosci.* 2015a;16:64. 26453336 10.1186/s12868-015-0203-1 4600218

Cossell *et al.* (2015) Functional organization of excitatory synaptic strength in primary visual cortex

Barth and Poulet (2012) [Experimental evidence for sparse firing in the neocortex](#)

Competing Interests: The authors declare no competing interests.

Reviewer Report 20 June 2016

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The manuscript by Bharmauria & Bachatene is a provocative opinion article that claims a role for a particular set of visual cortex neurons in mediating/maintaining some functional aspects of the organization of the visual cortex in response to external stimuli. The script is interesting, well written, and reviews the pertinent literature. It has potential implications in terms of neural circuitries computation of sensory information in the brain.

Using orientation columns as an experimental model, the authors propose that repulsive neurons may play an important role in the orientation processing by visual cortical neurons. The discussion is based on the emerging view that neuronal dendrites possess synapses corresponding to all orientation columns. The authors, however, fail to provide additional anatomical insights that may support their hypothesis. For instance, when thinking about neurons that learn orientation or repulsions shifts after adaptation, horizontal connections between spatially separated cortical areas represented by inhibitory interneurons that may ultimately influence synapses of dendrites of single units, immediately come to one's mind. Can the authors rule out this possibility? The work may also get insights from a description of experimental models designed to address the potential role of repulsive shifts in the preservation of the functional organization in the visual cortex.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 22 Feb 2017

Vishal Bharmauria, Université de Montréal, Montréal, QC, Canada

We thank the reviewer for his constructive comments on the manuscript. As suggested by the reviewer, we have added a paragraph that relates to the inhibitory neurons and horizontal connections in the cortex. Moreover, the role of repulsive neurons in maintaining the columnar organization after adaptation protocols, has also been added. We have also added a few references that suggest the role of repulsive neurons.

Competing Interests: The authors declare no competing interests.

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