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Review

Targeting the functional properties of cortical neurons using fMR-adaptation

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ABSTRACT

The introduction of functional brain imaging based on BOLD-fMRI, twenty years ago, has revolutionized the field of human brain research. However, right from its inception it became clear that the BOLD signal suffers from a serious limitation— it reflects the averaged activity of large neuronal populations and hence can not, on its own, index the functional properties of individual neurons. The method of fMR-adaptation (also termed repetition suppression) was developed to circumvent this problem and use the BOLD signal to assess functional specializations at the individual neuron level. The approach is based on the tendency of cortical neurons to reduce their activity upon stimulus repetition. By examining the sensitivity of the adaptation effect to stimulus manipulation, insight can be gained about the invariant and selective properties of neuronal networks. It has been argued that the adaptation effect occurs at the level of synaptic inputs— and hence may be mislocalized. However, it is critical to consider the adaptation effect in the context of the cortical network architecture. This cortical anatomical organization, dominated by short range intrinsic connections, ensures that the fMR-adaptation largely reflects the response profile of the neurons located within the imaged voxel proper.

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Contents

Introduction

With the advent of functional brain imaging using Magnetic resonance 20 years ago it quickly became evident that this method is going to dominate human brain research in years to come. In the visual domain, this method made it possible to map in great detail the layout of human visual areas (Tootell et al., 1996). Of particular interest was the discovery of a new cortical region that appeared to be a major player in human object recognition, termed the "Lateral Occipital Complex" (LOC) (Malach et al., 1995). The name anticipated, as indeed was born out by future research, that the Complex consists of a number of functionally distinct areas. However, a natural follow up of the LOC discovery required the examination of one of the hallmarks of recognition processes – their invariance to changes in optical stimuli – such as retinal position and size (see below).

Here a major, often overlooked, drawback of the fMRI method became evident: the BOLD signal reflects the averaged responses of a large number of neurons — (e.g. (Levy et al., 2004)). Such averaging is particularly problematic when attempting to interpret the "tuning" of BOLD responses in terms of the response profiles of the individual neurons in the imaged voxel (Grill-Spector and Malach, 2001).

To understand the inherent problem— consider the simplified model of an fMRI voxel illustrated in Fig. 1. Note that if the imaged voxel contains a heterogeneous and balanced mix of highly selective neurons, for example neurons narrowly tuned to image size, the BOLD response, which pools all these selective responses together, will consequently appear to be "size invariant" i.e. respond equally to all image sizes. The

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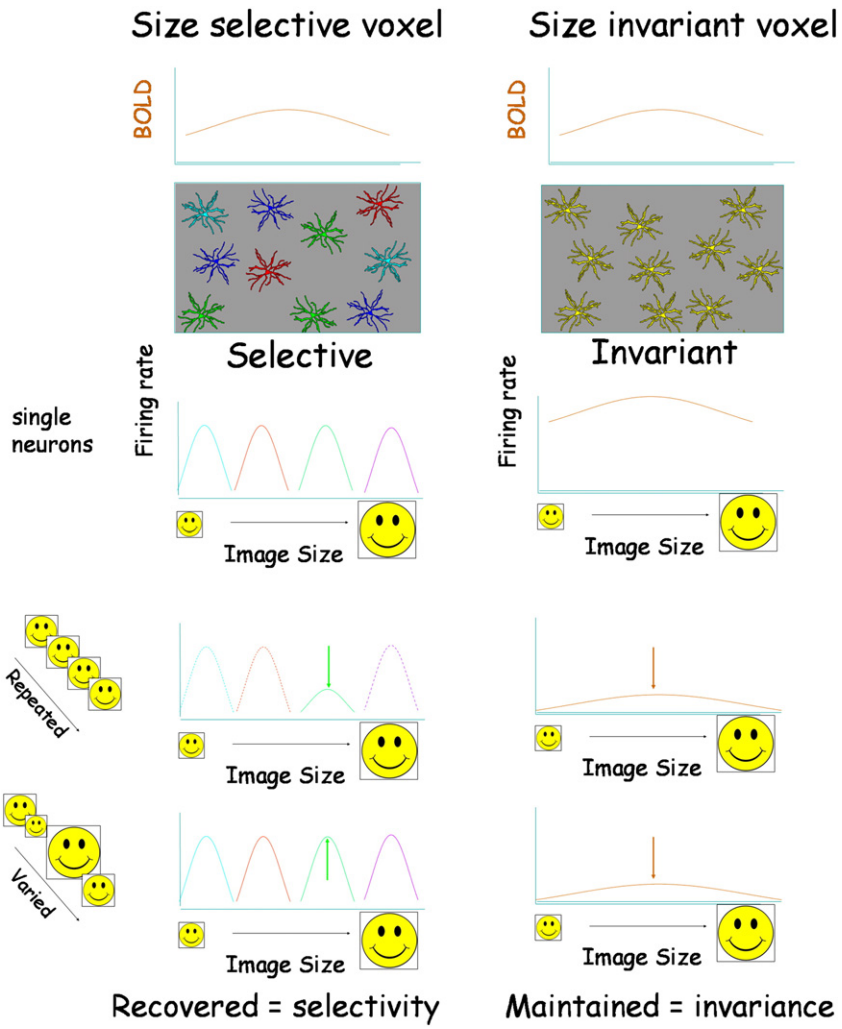

Fig. 1. Differential fMR-adaptation effects reflect the underlying neuronal selectivity. Schematic illustration of two hypothetical voxels in high order visual areas. The left row illustrates a voxel consisting of a balanced mix of neurons each narrowly tuned to a different image size (tuning curves for each neuron type illustrated in the "single neuron" panel). Note that unlike the individual neurons, the BOLD signal, reflecting the averaged response, shows a flat tuning — i.e. an erroneous "size invariance" (top panel). The voxel illustrated on the right consists of size invariant neurons. The BOLD tuning (top panels) can not differentiate between these two functionally distinct neuronal populations. However, the phenomenon of fMR-adaptation — i.e. the reduced neuronal activation upon stimulus repetition can uncover the functional distinction between the neurons comprising the two voxels. Note that when varying image size, the voxel on the left will show a recovery from adaptation, since the underlying neurons are sensitive to this manipulation, while the voxel on the right will remain in the adapted state since the neurons comprising it are "blind" to the size change.

same will be true, of course, if the neurons in the imaged voxels are individually size invariant— (Fig. 1 right panel). Thus, it is impossible to decide, by observing the BOLD response alone, what are the functional properties of the neurons comprising the imaged voxel. It is important to note that as long as the individual neurons are indeed invariant — this ambiguity can not be resolved at *any* resolution except the single cell level. Consequently, increasing the spatial resolution of the fMRI method e.g. by increasing field strength can not resolve this problem.

Importantly, the recently introduced approach of analyzing voxel patterns (Edelman et al., 1998; Haxby et al., 2001; Haynes, 2008; Kamitani and Tong, 2005), while highly successful in increasing our sensitivity to subtle signal changes, is still limited by spatial averaging at the single voxel level, and hence can not resolve this conundrum. To overcome this problem necessitated an alternative fMRI approach— one that was sensitive to the properties of the individual neurons rather than their summed response profile.

A potential way to circumvent this problem was suggested at the time by the report of familiarity effects in single neuron recordings in monkey infero-temporal cortex— a likely homologue of human LOC (Li et al., 1993). It was found that in a majority of recorded neurons, repeating a visual stimulus at a fairly short interval led to a significant reduction in neuronal firing. If such reduction could be observed in the BOLD fMRI response, this may offer a way to target the individual neuronal responses rather than the bulk activity. Thus, whether a neuron will respond to a series of stimuli as a repetition or not will depend on its functional selectivity irrespective of the population response— and this fact could then be utilized to index the "single neuron" properties in a group.

To illustrate this logic, consider the case of the visual neurons depicted in Fig. 1. We would expect that the neurons that are size invariant (right panel) will be "blind" to changes in the image size— i.e. they will treat size changes as if the stimuli were identical – a repeated image – and hence will undergo signal reduction. In contrast, the size-selective neurons (left panel) will recover — i.e. show a signal increase. This will occur because, for the individual neurons in this group, each size change appears as a novel stimulus and hence will interrupt the repetition effect. By comparing the signal reduction across neuronal groups and across image manipulations; we could potentially resolve the ambiguity concerning the invariant or selective properties of the underlying neurons. Thus, the repetition phenomenon offers a method for targeting the individual selectivity profile of neurons within the imaged voxel.

Indeed, a robust repetition reduction effect could be observed in high order visual areas (Grill-Spector et al. 1998). Furthermore, the effect could be productively used to examine perceptually-related invariances (see below). The term chosen for this phenomenon was fMR-adaptation. More recently the phenomenon has also been termed repetition suppression and even priming. Here I will use the original — "fMR-adaptation" throughout the text.

A comprehensive coverage of adaptation research is beyond the scope of this short review. Instead I will illustrate how the fMR-adaptation method has been implemented by reviewing a few examples of studies based on this approach. I will emphasize the aspects of invariance and selectivity in the visual system, but it should be noted that fMR-adaptation is a ubiquitous cortical phenomenon that can be utilized in non-sensory systems as well (e.g. (Dinstein et al., 2008)). I will then review briefly the likely mechanisms that underlie the adaptation effect with a special emphasis on whether such mechanisms affect our ability to localize the adaptation effects in cortical circuits.

Adaptation studies of neuronal invariance

The brain is bombarded by an enormous flow of information that needs rapid processing and response. An important solution to this challenge is generalization— the ability of brain circuits to group together different instances that share a common meaning into a single entity. This generalization ability, also termed "invariance", is of extreme importance and hence is ubiquitously reflected in brain systems. Furthermore, while we typically pay close attention to what brain neurons are "specialized" for – the complementary aspect – i.e. the nature of their functional generalization or invariance — is no less informative when trying to understand the computations and functional roles of specific cortical networks.

While the phenomenon of invariance is pervasive in many aspects of cognition, here I will focus on the human visual system since it provides some of the best examples of stimulus invariance, and also some of the brain imaging challenges where neuronal adaptation can be particularly informative. An important role for invariance in the visual domain concerns object recognition – for example, in allowing us to identify a person or an object despite substantial changes in optical parameters – such as retinal position, direction of illumination, image size etc. It is important to emphasize that to the extent that such invariances are reflected in visual perception – for example in the stability of the perceptual image despite saccadic eye movements – such generalizations can assist in identifying neuronal mechanisms underlying perceptual awareness. Thus, considering the example of perceptual stability, it is likely that neurons showing invariance to retinal position are more closely associated with perceptual awareness than those retinotopically selective neurons that incessantly modulate their activity any time the eye moves.

Thus, neuronal invariance is an exceedingly informative aspect of cortical functionality. How then can we study it in the human brain? The most straightforward means is to examine the tuning curves of individual neurons under different stimulus manipulations. In non-human primates such approach has indeed led to many insights concerning neuronal invariance— for example single unit recordings in primate IT have revealed size and position invariance (Ito et al., 1995; Sary et al., 1993). More recently, employing an elegant combination of fMRI and single unit recordings (Freiwald and Tsao, 2011) demonstrated clear examples of viewpoint invariance of single neurons in the anterior face patch of monkey IT.

In the human brain however, such single unit recordings are extremely rare and have been obtained only in the course of clinical diagnostic procedures in epileptic patients. However, this data has been confined so far to areas beyond the visual system proper-such as medial temporal lobe structures (e.g. (Gelbard-Sagiv et al., 2008; Quiroga et al., 2005). Thus, the only method that is currently feasible for studying neuronal invariance in the human visual system is fMR-adaptation.

As discussed above, the adaptation approach has been originally adopted successfully to study neuronal invariance in the study of object representations in human high order visual areas. Thus, (Grill-Spector et al., 1999) were able to demonstrate that neurons in the human fusiform gyrus are invariant to small position, view-point and size changes (Grill-Spector et al., 1999). FMR-adaptation was used to demonstrate that neurons in high order object areas (the Lateral-Occipital Complex) are invariant to changes in low level features of visual stimuli (Kourtzi and Kanwisher, 2001). In the fusiform "Word Form Area" (Cohen et al., 2000; Hasson et al., 2002) a region selective to letter and word forms— adaptation effects were employed to demonstrate invariance across different fonts when representing identical words (Dehaene et al., 2001).

Neuronal invariance was also found to provide important insights into the distinct specializations of cortical networks. Such invariance-based specializations were used to explore the functional distinctions between the dorsal and ventral visual steams — which have been a pivotal concept in primate visual system organization (Haxby et al., 1991; Mishkin et al., 1983). In correspondence with the roles of the dorsal (spatial/"where") pathway in action and the ventral (shape/"what") pathway in recognition — adaptation studies were used to demonstrate different kinds of invariance in the two streams— with the dorsal stream showing invariance to object identity while ventral stream areas showing invariance to spatial orientation and type of motor action (Shmuelof and Zohary, 2005; Valyear et al., 2006). In summary— since its introduction, fMR adaptation has been used fruitfully to expand our understanding of the functional aspects over which neurons generalize in a variety of areas and cognitive tasks.

Adaptation studies of neuronal selectivity

The complementary aspect of neuronal invariance is that of neuronal selectivity. As discussed above, if individual neurons are narrowly tuned to a certain parameter — we would expect a "release" from adaptation as we change the input along the tuned dimension (see Fig. 1 left panel). However, in contrast to the case of neuronal invariance, when the BOLD signal shows a stimulus selective responses— one can safely infer that the single neurons contributing to the BOLD are also selective. This is a consequence of the simple fact that as in any group response, the population averaging that generates the fMRI signal can only broaden the tuning curves of the individual neurons comprising the imaged voxel.

Indeed, such logic underlies the rapidly expanding and highly successful field of multivariate pattern classifier fMRI. Although this approach is based on direct BOLD signal measures, which by necessity reflect the averaged selectivity profile of neuronal groups, its ability to detect subtle selectivities in such groups provides an upper bound on the tuning width of individual neurons in the imaged voxels (e.g. (Edelman et al., 1998; Haxby et al., 2001; Haynes, 2009; Kamitani and Tong, 2005).

The adaptation approach could provide a sensitive window into neuronal selectivity that could extend the information obtained from such spatio-temporal pattern analysis approaches. Indeed a number of insights concerning functional selectivity have been obtained using fMR-adaptation. A particularly important observation concerns the selectivity to individual exemplars in face-related brain regions such as the FFA. With the original characterization of face related regions in the human cortex using BOLD, (Haxby et al., 2000; Kanwisher et al., 1997) the emphasis was on the category preference of these areas rather than their selectivity to individual faces. By contrast, individual face identity in face areas has been consistently highlighted by fMR-adaptation. This exemplar sensitivity of fMR-adaptation was reflected in the release from adaptation when presenting a series of different

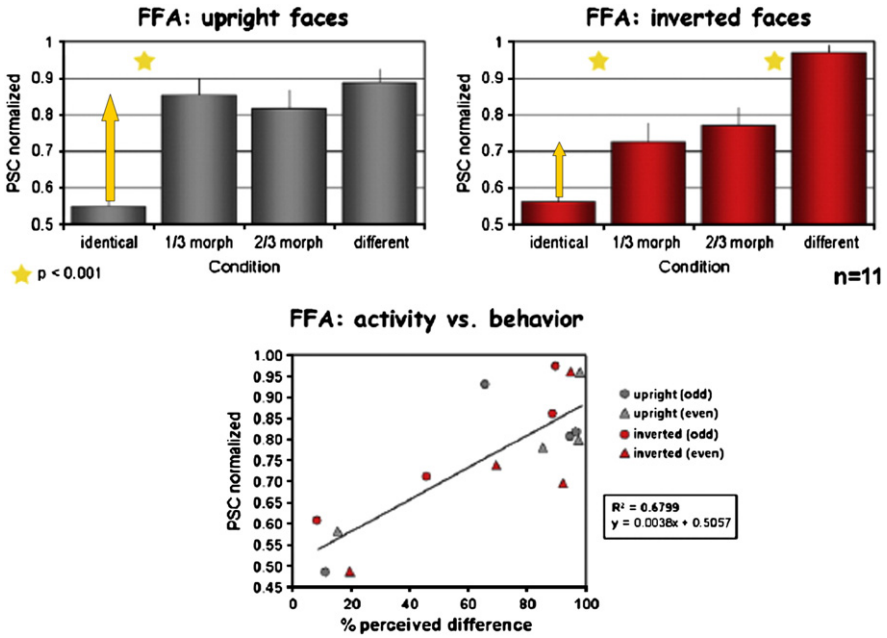

Fig. 2. Adaptation effects uncover mechanisms underlying perceptual similarity. Bold responses in the fusiform face area to a series of identical face images (identical), 1/3 and 2/3 level morphs (between a target face and other faces) as well as a series of different face exemplas. Note that in the case of upright faces, the release from adaptation occurred with minimal morphing (top left panel, arrow), while in the case of inverted faces the release was more gradual (top right panel, arrow) even though the physical difference between the images was identical in the upright and inverted conditions. Importantly, the release from adaptation was correlated to subjects' ability to perceptually detect the changes in face identity— suggesting that perceptual face discrimination is grounded in the shape tuning of individual neurons.
Modified from Gilaie-Dotan et al. (2010).

face exemplars (Grill-Spector et al., 1998). Interestingly, recent BOLD imaging studies using a pattern classifier approaches has succeeded in providing hints of such exemplar selectivity in direct BOLD signals (Kriegeskorte et al., 2007; Nestor et al., 2011). Adaptation has been further used to gain insights into the nature of such exemplar selectivity. For example, whether norm-based models (Leopold et al., 2006) may guide representations of individual faces in human face areas (Davidenko and Grill-Spector, 2010).

Examining the adaptation effects to morphed face images, both upright and inverted, (Gilaie-Dotan and Malach, 2007; Gilaie-Dotan et al., 2010) found that release from adaptation correlated with the ability of subjects to perceptually discriminate between different faces (see Fig. 2). This result suggests that our ability to distinguish individual faces is likely grounded directly in the tuning width of individual neurons rather than derived from some computations between broadly tuned face-category neurons. Another relevant observation was made by (Axelrod and Yovel, 2011) showing that adding a non face element such as glasses to a face was sufficient to bring about a release from adaptation— again hinting that face neurons are narrowly tuned to holistic images that are perceptually discernable.

Finally, in an elegant application of the adaptation approach —(Large et al., 2008) were able to tie neuronal adaptation to perceptual awareness. Examining the visual phenomenon termed "change blindness" they found that release form adaptation in ventral stream areas was tied to the ability of subjects to detect optical changes introduced to a series of rapidly flashed images. In contrast, when subjects failed to detect such changes, adaptation persisted.

Adaptation mechanism and their implications

So far I have focused on the adaptation phenomenon as a tool in deciphering individual neuronal properties underlying the fMRI voxel responses. However, an important issue concerns the nature of the neuronal mechanisms that produce the adaptation effect itself. This is significant both because adaptation is an interesting cortical phenomenon in its own right, but also because understanding its underlying mechanism is necessary to properly interpret the meaning of adaptation results. A number of recent studies indeed examined the neuronal mechanism of fMR-adaptation and a thorough discussion of this issue can be found in (Grill-Spector et al., 2006). Here I will focus on the possible implications that accepted models of neuronal adaptation may have on our ability to interpret, and in particular to properly localize, the neurons whose functional properties are uncovered by the adaptation effects.

A clear consensus regarding the neurophysiological mechanism(s) underlying fMR adaptation is lacking. A simple possibility is that the adaptation is an aspect of attentional modulation. Thus, it could be argued that a stimulus becomes "boring" upon repetition, leading to reduced attention which in turn reduces the BOLD signal. However, studies in which attention was carefully controlled or manipulated argue against this conclusion— showing that under certain conditions, attention and adaptation effects can be dissociated (Xu et al., 2007). Furthermore, adaptation effects have been demonstrated even under subliminal viewing conditions, when subjects were unaware of the adapting stimuli (Dehaene et al., 2001). However, even though attention does not seem to underlie the adaptation effect, it is likely to play an enabling role— i.e. focused attention may be required for adaptation to occur. For example, if adaptation necessitate a minimal level of neuronal activation (Avidan et al., 2002), then diverting attention away from the adapting stimulus may reduce neuronal responses to such a degree as to abolish the adaptation process.

Under the reasonable assumption that human fMR-adaptation is at least qualitatively similar to adaptation phenomena observed in monkey cortex (Li et al., 1993) as well as in other mammalian species— a number of single neuron studies offer relevant insights. One mechanism that these studies point to is synaptic depression or "fatigue" (Grill-Spector et al., 2006; Katz et al., 2006; McMahon and Olson, 2007).

It has been argued that if a substantial factor in fMR-adaptation is some sort of synaptic depression, this may limit our ability to localize

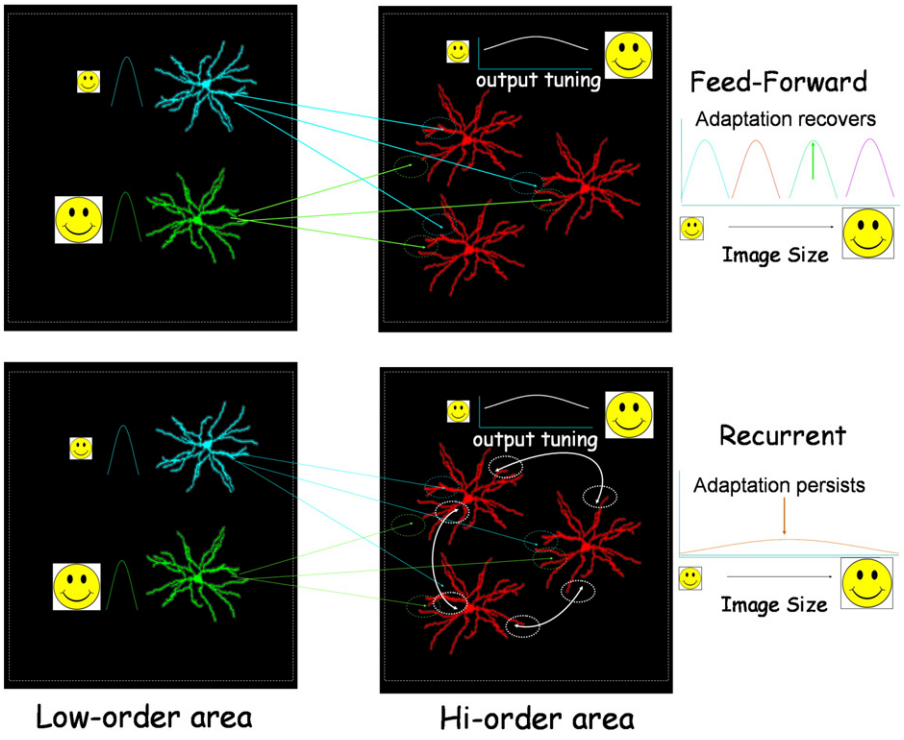

Fig. 3. The role of cortical architecture in co-localizing the adaptation effect. The figure illustrates the cases of feed-forward (top) and recurrent (bottom) connectional architectures. In both cases size-selective inputs from low-order cortical regions (left panels) converge to produce size invariant neurons in a high order area (right panels). In the case of the feed-forward architecture (top right panel), the input synapses, where adaptation presumably occurs, show size selectivity (colored dotted lines). However, in a locally recurrent network (bottom right panel) input and outputs intermingle due to the local connectivity (white arrows). In such networks the adaptation effects and neuronal activity will co localize (white dotted lines).

the adaptation effect. (Sawamura et al., 2006), see also Fig. 3 top panels). The mislocalization is due to the fact that the synaptic inputs actually reflect the properties of neurons upstream to the recorded area. Thus, for example, neurons in non-face regions of human cortex, which receive inputs from the fusiform face area—, may show face-specific adaptation, not because the neurons in this area are face-specific, but because they "inherit" the adaptation effect from their neuronal afferents. Interestingly, a similar concern has been expressed with regards to the BOLD signal itself: given that the neuro-vascular coupling is likely driven by synaptic mechanisms, one would expect the BOLD response to represent the inputs to a cortical region- derived from voxels upstream to the imaged voxel (Logothetis et al., 2001). When considered in the case of specifically uni-directional connections, i.e. when the inputs to a cortical area are sent from a remote anatomical distance, this model, both as it pertains to the BOLD response in general and to fMR-adaptation in particular is indeed valid. Note that in such feed-forward architecture, the neuronal properties of the source voxel will lead to adaptation effects that will indeed be erroneously displaced to the imaged voxel (Fig. 3, top panels).

However- it is important to consider the adaptation effect in the more realistic architecture of dense cortical networks. Tract tracing studies, as well as recording in cortical slices consistently reveal a massive level of local synaptic connectivity— in which the main outputs of cortical neurons are not sent to a remote external target but impinge locally upon neighboring neurons (Fig. 3, bottom panels). This phenomenon is particularly prominent in high order cortical areas, where, interestingly, adaptation effects are most prominent (Amir et al., 1993; Grill-Spector and Malach, 2001). In such locally interconnected systems, most input synapses actually emanate from neighboring neurons within 1–2 mm —a distance corresponding to a typical size of an fMRI imaged voxel, (Amir et al., 1993; Douglas and Martin, 2004; Nir et al., 2008). In other words, the large majority of synaptic inputs impinging on cortical neurons reflect the functional properties of the neurons in the imaged voxel itself. To the extent that fMR-adaptation reflects the properties of these synaptic inputs, we would expect that the adaptation effect in the locally reverberating cortical networks would therefore reveal the functional selectivity of the neurons comprising the imaged voxel itself (Fig. 3, bottom panels).

This conclusion has been supported by the demonstration of orientation selective adaptation in primary visual cortex (in which the thalamic inputs are non oriented) (Tootell et al., 1998), and more generally by a number of studies of the BOLD response proper (Kang et al., 2010: Mukamel et al., 2005; Nir et al., 2007; Tsao et al., 2006). Thus, given the unique, locally interconnected cortical architecture, we can safely co-localize the neuronal firing rates, the BOLD response and the adaptation effects to the same imaged voxel.

Comparing fMR-adaptation and pattern classifier approaches

Recently, there has been a growing interest in examining BOLD responses, not merely as averaged activations in a set of voxels but at the level of response patterns in clusters of voxels. Such "multivariate" pattern classifier approaches have indeed proven to be more sensitive — revealing subtle neuronal selectivity which the more conventional univariate analysis failed to detect (e.g. (Kamitani and Tong, 2005). Given the sensitivity of multivariate approaches— they could offer means to cross-validate fMR-adaptation results. Unfortunately, only few comparisons of the two methods exist so far (Sapountzis et al., 2010). However, one can gain some insights by comparing studies in which adaptation and pattern classifier analysis were applied to similar brain areas. Here I will mention two such instances.

A particularly robust and ubiquitous phenomenon revealed by fMR-adaptation is the exemplar selectivity of neurons in high order object areas (Grill-Spector et al., 1999) This finding has now been nicely

corroborated in pattern classifier studies of object representations— which have clearly documented such exemplar selectivity in the patterns of voxel responses (Haushofer et al., 2008). Interestingly, an early pattern classifier study failed to detect exemplar selectivity for faces in the fusiform face-area— (Kriegeskorte et al., 2007) a finding which appeared to contradict the results of fMR-adaptation which showed clear exemplar selectivity in face areas (Gilaie-Dotan et al., 2010). However, more recently an indication for exemplar selectivity for faces was described using pattern classifier approaches in the FFA as well (Nestor et al., 2011)— thus providing additional confirmation for the sensitivity of the fMR-adaptation method.

Another domain where pattern classifiers could be compared to fMR-adaptation is the case of stimulus position. Adaptation effects in the LO subdivision of the LOC has revealed a release from adaptation when stimuli shifted their location relative to fixation (Grill-Spector et al., 1999) although this region has not been originally defined as retinotopically organized (Sereno et al., 1995). However, here again there appears to be an agreement between more recent pattern classifier analysis and the adaptation results— both showing sensitivity to object position in LO (Cichy et al., 2011).

Thus, it appears that in the few cases where pattern classifiers and adaptation effects could be compared, both methods reveal compatible results, further corroborating that fMR-adaptation can provide a proper localization of neuronal properties.

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