

Functional Magnetic Resonance Adaptation in Visual Neuroscience

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SYNOPSIS

Functional magnetic resonance imaging (fMRI) is a powerful non-invasive tool to investigate neuronal processing. In the last ten years a new methodological approach in the field of fMRI has been developed: fMRI adaptation. It has been found that the repetition of a stimulus leads to a decrease of the fMRI signal in the brain region that processes this stimulus. The phenomenon has been related to neuronal adaptation effects found in single-cell recordings. Since the first experiments that observed fMRI-adaptation effects, the method has been applied extensively to study various visual phenomena, such as the perception of motion, shape, objects, and orientation. The great advantage of fMRI adaptation is that it allows assessing the functional response profile of a brain region at a subvoxel level. The purpose of the current review is to evaluate the different experimental approaches used to elicit fMRI-adaptation effects. We discuss papers published in the domain of visual neuroscience that made use of fMRI-adaptation paradigms. In doing so, we focus on methodological considerations concerning experimental design, stimulus presentation and influencing factors such as awareness and attention. In the course of this review, we show that different fMRI-adaptation designs capture heterogeneous neuronal adaptation effects. As the picture of the mechanisms underlying neu-

ronal adaptation changes from simple synaptic fatigue to complex network interactions, the concept of fMRI adaptation has to be redefined.

KEY WORDS

neuronal adaptation, repetition suppression, neural attenuation, priming, BOLD decreases, neuronal fatigue, experimental design, attention

INTRODUCTION

From the start of functional magnetic resonance imaging (fMRI), signal attenuation due to prolonged stimulation has been observed (Fig. 1A) (3,26,95). In the following years, researchers from the field of perceptual memory and priming (8,9,90) were the first to notice fMRI signal decreases when comparing the repetition of a stimulus to the presentation of two different stimuli (Fig. 1B). In their seminal work on visual object priming, Buckner *et al.* (9) demonstrated decreased fMRI signals in extrastriate visual cortex following the brief, repeated presentation of visual objects. Furthermore, the repeated presentation of visual objects also led to behavioral priming effects; ever since then, it has been argued that decreased fMRI signals due to repetition might be the neuronal correlate of behavioral priming effects. In direct succession, Grill-Spector and colleagues (28) studied repetition-related fMRI-signal decreases to infer the selectivity of a specific visual brain region for a stimulus feature. This can be accomplished by first adapting a specific neuronal population (e.g., orientation-selective cells in primary visual cortex [V1]) with a repetitive presentation of a specific stimulus (e.g., a vertical grating). In a second step, the stimulus is varied along a predefined dimension (e.g., orientation) and the fMRI response to this change of the visual region under study is assessed.

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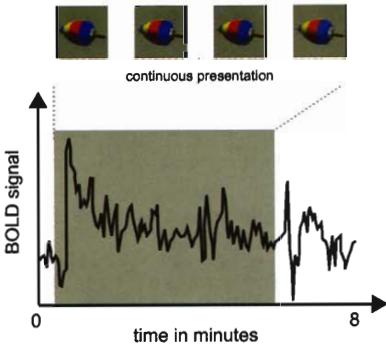
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A FMRI adaptation after prolonged stimulation



B FMRI adaptation after repeated stimulation

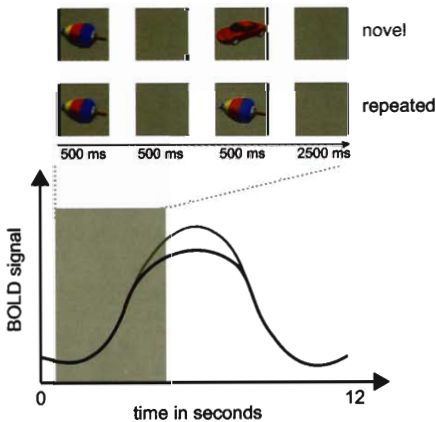


Fig. 1: fMRI adaptation. **A.** Schematic illustration of the adapting fMRI signal due to prolonged stimulation (over minutes). (Adapted from Human Brain Mapping, Vol. 5, No. 2, 1997, 93-109; © 1997 by Wiley-Liss, Inc. Reprinted with the permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.) **B.** Schematic illustration of a short-lag adaptation effect based on stimulus repetition that can be observed at the fMRI signal time course. (Object images courtesy of Michael J. Tarr, Brown University, <http://www.tarrlab.org/>)

It is argued that, if the underlying neuronal population is indifferent to the change of the stimulus (does not exhibit orientation selectivity), the fMRI signal will be reduced similarly to the repetitive stimulation with the identical stimulus. On the contrary, if the neuronal population is sensitive to the change (does exhibit orientation selectivity), a rebound from adaptation will be observed: the signal will return to the non-adapted level. Based on this rationale, the technique of fMRI adaptation has become a powerful tool to characterize the functional profile of brain regions. Most importantly, fMRI adaptation is thus able to reveal response properties of neuronal populations at subvoxel resolutions.

The popularity of the method of fMRI adaptation is reflected in a large number of studies that made use of fMRI-adaptation effects, and several recent reviews summarizing the field /30,59/. The phenomenon is most commonly referred to as 'fMRI adaptation' /7,20,24,40,52,60,104,106/ or 'repetition suppression' /17,33,36,45,82/; both terms strongly relate to neuronal adaptation effects that have been observed in electrophysiological recordings /61,67,79,87/. Until today, however, the underlying neuronal mechanisms of fMRI adaptation are still not fully understood. More descriptive terms have also been used, such as 'repetition attenuation' /97,98,110,111,112/ and 'repetition-related response reduction' /113/. We will adhere to 'fMRI adaptation' since it captures the correspondence of fMRI and neuronal adaptation effects /61,67,79,87/. More precisely, we will use the term 'fMRI adaptation' to name the technique, and the term 'fMRI-adaptation effect' to refer to the observable fMRI signal decreases.

Interestingly, as diverse as the naming of the phenomenon are the experimental approaches that aim at eliciting fMRI-adaptation effects. Thus, a first goal of this review is to sort the different experimental designs in use and to compare their efficiency of evoking fMRI-adaptation effects. In addition, we address in detail the most important design factors, such as repetition lag, adaptation duration, number of repetitions, visibility, and attention. Based on these reflections, we argue that different experimental designs most likely target different neuronal adaptation processes. We further

elucidate this finding by referring to electrophysiological investigations that studied neuronal adaptation.

EXPERIMENTAL DESIGN

Starting with those studies that explicitly made use of fMRI adaptation as a specific marker of neuronal processing and inspecting the underlying experimental designs we found that almost all study designs can be assigned to one of six different types (Fig. 2). In the following we describe those different design types on the basis of original experiments. We also report which other studies employed the respective design and comment on why a specific design type might be appropriate for the study of specific features.

Block design with different numbers of repetitions

One of the classical studies in the field of fMRI adaptation is the investigation by Grill-Spector and colleagues /28/. Their use of an fMRI-adaptation approach was motivated by the need to circumvent the spatial limitations of conventional fMRI methods in order to resolve the response properties of neuronal populations at a subvoxel level. Using conventional fMRI methods it was not possible to disentangle neuronal populations that, e.g., would code for different object views within one imaging voxel. Grill-Spector *et al.* /28/ employed an experimental design that we will call 'block design with different numbers of repetitions' (Fig. 2A). The primary idea behind this design is that the amount of signal decrease relative to a non-adapted reference activation should vary as a function of number of repetitions. Grill-Spector and co-workers /28/ repeated either the same object 32 times in a block, 16 times intermixed with one other object, 8 times intermixed with three other objects, 4 times intermixed with seven other objects, or they presented 32 different objects. They found clear fMRI-adaptation effects when objects were repeated (32 times or 16 times) in comparison to the blocks containing 32 different images in the ventral visual pathway /28/.

Other studies employed similar experimental designs /65,112/. Block designs with different num-

bers of repetitions were also applied in a study investigating fMRI-adaptation effects across species /80/ and, by the same group, in a neurophysiological single-cell study /81/. Sawamura *et al.* /80/ revealed highly similar fMRI-adaptation effects to repeated objects in macaques and human subjects. Secondly, testing the design in their single-cell study led to robust neuronal adaptation to repeated objects in the IT cortex of the macaque /81/, demonstrating a good correspondence between fMRI and neuronal adaptation.

Block design with image variation

In the same study reviewed before, Grill-Spector *et al.* /28/ also applied what we will call a 'block design with image variation' (Fig. 2B). In such a design, different blocks are contrasted, where all blocks involve the repeated presentation of a stimulus, but with different variations of stimulus dimensions such as size, position, viewpoint, and illumination. For example, Grill-Spector contrasted blocks in which a face was repeated with fixed illumination with blocks in which illumination of the same face (identity preserved) was changed from instance to instance /28/. Thereby, the authors were able to show that subparts of the lateral occipital complex (LOC) show some invariance to size and position changes, but less so to illumination and viewpoint changes (for an extensive review of these findings see /29/). Other investigators employed a block design with image variation to study viewpoint effects on object representations /44/, direction-selective adaptation /74/, size and viewpoint effects on face representations /1/, place representations /23/, and response priming /13/.

Event-related design with pre-adaptation block

Another classical study was conducted by Buckner and colleagues /9/. They employed what we will call an 'event-related design with pre-adaptation block' (Fig. 2C). First, they presented a series of different object stimuli. They then showed the same objects again, intermixed with novel objects and fixation trials. Buckner *et al.* found fMRI-adaptation effects for repeated objects in comparison to novel objects in extrastriate areas, left dorsal prefrontal cortex, and anterior cingulate

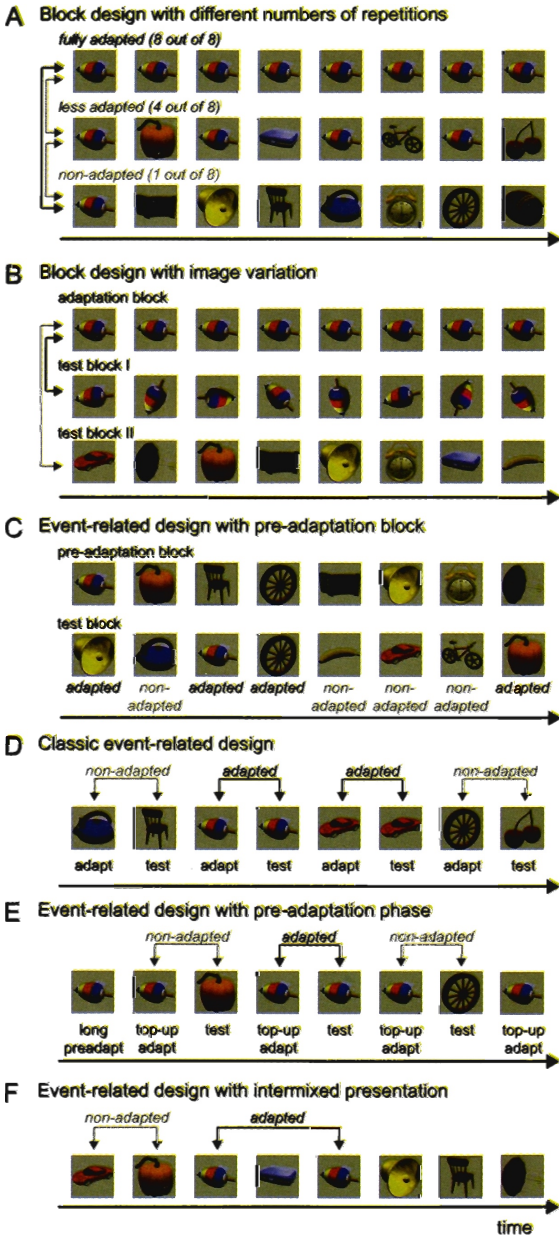


Fig. 2: fMRI-adaptation designs. A-F. Schematic illustrations of the different experimental designs that are used to elicit fMRI adaptation effects. Stimulus presentation is shown against time, and adaptor and test images/blocks are indicated. (Object images courtesy of Michael J. Tarr, Brown University, <http://www.tarrlab.org/>)

/9/. Furthermore, they also observed behavioral-priming effects as measured by decreased reaction times for repeated objects in comparison to novel objects /9/.

Because the repetition lag between the first presentation of the object and the repeated presentation is typically of the order of many seconds up to minutes and even days /100,101/, this design is thought to reveal rather long-lag adaptation effects. Those repetition effects are thought to be of cognitive nature, revealing processes of semantic memory more than stimulus-driven adaptation. Following the work by Buckner and colleagues /9/ the event-related design with pre-adaptation block has been used to investigate perception of faces /18/, places /22/ and objects /10,27,42,43,45,57,86,100,101,102,108/.

Classic event-related design

Most studies in the fMRI-adaptation field use what we call a 'classic event-related design' (Fig. 2D). Every event consists of a rapid presentation of two consecutive stimuli that are only separated by a brief interval or none. The adaptor image is always tested immediately. Thus, the classic event-related design is thought to be the only design that identifies very short-lag adaptation effects. A paradigmatic study that made use of a classic event-related design was conducted by Kourtzi and Kanwisher /52/. They tested whether line drawings and grayscale photographs of objects are represented by the same neuronal subpopulation in LOC or by different populations /52/. During scanning subjects were presented two images that depicted either the same object or different objects and that could be either of the same format (line drawing or photograph) or in different formats. Kourtzi and Kanwisher /52/ found fMRI-adaptation effects in the LOC to the repetition of identical objects independent of their format and concluded that the LOC represents perceived shapes. Extending their own findings in further studies on object recognition always employing classic event-related adaptation designs /53-56/, Kourtzi and colleagues strongly fostered the short-term adaptation technique. Many researchers followed /2,7,15-18,21,22,25,46,58,70,71,77,81,99,104,106,107,110/. The classic

event-related design has also been tested in a recent electrophysiological single-cell study /81/. There it was found that the design is able to elicit neuronal adaptation in neurons of IT cortex to repeated objects /81/. Thus, we may conclude that the rapid event-related design reliably detects fMRI-adaptation effects in extrastriate cortex.

It has been debated to what degree fMRI-adaptation effects measured with event-related designs can be explained either by neuronal adaptation effects or non-linear neurovascular coupling /7/. As with every rapid event-related design the challenge is in determining the fMRI signal corresponding to a single event (trial) out of the highly convoluted signal time course. First estimations have suggested that fMRI signals add up almost linearly /6,12/. However, a study by Huettel and McCarthy /38/ revealed that the response to a second stimulus following a first stimulus is significantly smaller than would be expected based on the assumption of linearity. Subjects were presented identical high-contrast checkerboard stimuli that were separated by interstimulus intervals of 500, 1,500, 3,500 or 5,500 ms while scanning. Huettel and McCarthy assessed the fMRI signal along the calcarine sulcus by subtracting the response to the pair of stimuli from the response to a single stimulus. They found that the response to the second stimulus decreased in amplitude and increased in latency with shorter repetition delays. Huettel and McCarthy attributed the observed non-linearity to a 'refractory period' in the fMRI hemodynamic response /38/.

Direct empirical evidence that part of this non-linearity is indeed based on neuronal adaptation effects came from a study by Boynton and Finney /7/. They investigated orientation-specific adaptation since it is known that early visual areas contain orientation-specific neuronal subpopulations. By presenting either two gratings of the same orientation or two differently oriented gratings in rapid succession, Boynton and Finney /7/ found fMRI adaptation to repeated orientations in visual areas V3 and V4 (but not in V1/V2 - see the following section on event-related designs with pre-adaptation phase for a possible explanation). At the same time, they tested contrast adaptation behaviorally as an indirect measure of neuronal adaptation. Further

evidence that part of the non-linearities caused by rapid event-related designs are based on neuronal adaptation effects came from a study by Heckman *et al.* /31/. They modeled the effect of a fast design as a scaling of stimulus strength, which has been shown to be a typical consequence of neuronal adaptation. In addition, they could almost abolish non-linearities by using stimuli that would produce minimal adaptation effects.

We conclude that fast event-related designs are capable of detecting adaptation effects. Part of the non-linearity observed with rapid stimulation sequences can be attributed to adaptation, given the stimulation is well controlled (e.g., balancing trial history). Still, it is important to note that the design was unable to reveal orientation-dependent adaptation effects in V1 and V2 and that such null effects pose a challenge to the interpretation of fMRI-adaptation effects.

Event-related design with pre-adaptation phase

An event-related design with pre-adaptation phase starts with a prolonged presentation of the adaptor stimulus over several seconds: 20 s /24/, 25 s /25/, 40 s /62/, 60 s /19,20/, 100 s /60,68/, or even 150 s /48/. Following this pre-adaptation phase is a classic event-related design in which the adaptor stimulus is now a so-called 'topping-up'-stimulus - the same stimulus as of the pre-adaptation phase shown again - followed by the test stimulus (Fig. 2E). The major differences from an event-related design with pre-adaptation block are that (1) the pre-adaptation phase is directly followed by the classic event-related design while in studies with a pre-adaptation block the block can be presented long before the actual event-related experiment, (2) studies using a pre-adaptation block focus more on cognitive effects related to semantic priming, while studies employing a pre-adaptation phase are more interested in perceptual adaptation phenomena elicited with these longer adaptation phases, and (3) in the event-related design with pre-adaptation phase, the adaptor is repeated before every test stimulus ('topping-up stimulus'). Although the topping-up stimulus and test stimulus immediately succeed each other, this design type is thought to reveal mid- to long-term adaptation effects depen-

dent on the pre-adaptation phase /59/. This type of design was adopted by several investigators to study fMRI adaptation in early visual cortex to orientation /20,24,48,60,68/ and color /19,20/. To our knowledge, there are only two studies that employed a pre-adaptation phase in the study of higher-level vision such as the perception of faces /25,73/.

In the case of orientation-dependent fMRI adaptation, the event-related design with a pre-adaptation phase has proven to be the only design capable of detecting orientation-dependent fMRI adaptation in V1. Attempts to detect adaptation effects to oriented gratings in V1 using classic event-related designs failed /7,71/. In a thorough investigation, Fang and co-workers /24/ directly compared the classic event-related design with the event-related design with pre-adaptation phase in the course of a study on orientation tuning in V1. They were able to reliably find orientation-dependent fMRI adaptation in V1 as well as in visual areas V2, V3, V3A, and hV4 when using the event-related design with a pre-adaptation phase of 20 s followed by topping-up stimuli of 5 s and test stimuli of 1 s presentation duration. Without the pre-adaptation phase and with short presentation durations of the adaptor stimulus for 1 s, however, they were only able to reveal orientation-dependent fMRI adaptation in V3A and hV4 /24/. One possible explanation might be that primary or early visual cortex is less susceptible to adaptation in general. Interestingly however, three research groups /56,71,104/ were able to demonstrate spatially selective fMRI-adaptation effects - that is fMRI-adaptation effects to retinotopic position - in V1 with classic rapid event-related designs.

In the case of fMRI adaptation to color, the studies so far /19,20/ used only pre-adaptation phases plus rather long presentation durations of the adaptor stimulus. The authors demonstrated fMRI adaptation in V1 to repeated red-green gratings as well as to repeated black-white gratings, while cross-adaptation (red-green/black-white or black-white/red-green) was clearly weaker. Because these were the only studies on color adaptation, it is unclear whether adaptation to color in V1 can be detected with a classic event-related design.

Fang and colleagues compared the classic event-

related design with the event-related design with pre-adaptation phase in a study on face perception /25/. They investigated the effect of viewpoint on face representations. Most importantly, the two different experimental designs revealed different viewpoint effects on adaptation. With the event-related design with pre-adaptation phase face-selective areas showed a graded viewpoint tuning, i.e., strongest adaptation for identical faces, less adaptation for 30 degrees rotation and even less adaptation for 90 degrees rotation. With the classic event-related design, the same regions showed strongly viewpoint-selective fMRI adaptation, that is adaptation for identical faces, but not for 30 degrees or 90 degrees of rotation /25/. The opposite effect was observed in parahippocampal cortex: Epstein and colleagues /22/ found viewpoint-dependent fMRI-adaptation effects with a classic event-related design, whereas they observed viewpoint-invariant fMRI-adaptation effects using an event-related design with pre-adaptation. In summary, also in higher-level visual processing, such as the perception of faces or places, the use of different designs might unravel different underlying neuronal processes.

Event-related design with intermixed presentation

During an event-related design with intermixed presentation, stimuli are presented in rapid succession. Some of the stimuli are repeated, some will occur only once. The repetition delay between the first presentation of the stimulus and its repetition is variable (Fig. 2F). It can vary between 0 s (immediate repetition) and several seconds up to minutes. It is important to note that other stimuli are presented during the delay phase; and that the delay is not simply filled with a fixation period. One of the studies that applied an event-related design with intermixed presentation delays is a classical study by Henson and colleagues /32/. They presented familiar and unfamiliar faces and symbols and found fMRI-adaptation effects for familiar faces and symbols in ventral visual areas, while unfamiliar faces and symbols led to repetition enhancement /32/. An advantage of this design type is that it allows addressing the question whether repetition-related adaptation effects depend on repetition lag. It should be noted, however, that

while some studies using an event-related design with intermixed presentation explicitly tested lag effects on adaptation /32,36,78,82/ others did not /33,37,41,47,98,102,109,111/.

In summary, it seems that the occurrence or non-occurrence of fMRI-adaptation effects critically depends on the interaction between design, visual area, and visual feature under study. This is an interesting first hint that although with every experimental design reported here one is able to elicit fMRI-adaptation effects, they might not all reflect the same underlying neuronal effect. Beyond the varieties in experimental design *per se*, the major difference between fMRI adaptation studies is in the repetition delay between the first presentation of a stimulus and its repetition. Shortest delays occur in classic event-related designs, while the longest delays were employed in event-related designs with pre-adaptation blocks.

STIMULATION PARAMETERS

In the following paragraphs, we report studies that investigated the effect of different stimulation parameters on fMRI adaptation. More precisely, we focus on effects of repetition delay - the delay between the first stimulus (adaptor) and second stimulus (test) - and stimulus duration. We report studies that investigated the effects of delay and stimulus duration within one experimental design. For easy comparison, we converted the reported repetition delay measurements (stimulus onset asynchronies, inter-pair interval) into measurements of interstimulus interval (ISI), that is the time between the offset of one stimulus and the onset of the following stimulus. Thus, when we refer to repetition delay, this equals ISI.

Repetition delay

Several studies have investigated the effect of repetition delay on fMRI-adaptation effects. First, we discuss short repetition delays that range from 0 to 7 seconds. Second, we cover studies that investigated middle (8 seconds to minutes) to long (minutes, hours, days) delays. Finally, we report on three studies that directly compared short with middle and long repetition delays.

Short repetition delays (0-7 s)

Boynton and Finney /7/ investigated orientation-specific fMRI-adaptation effects in early visual areas using ISIs that ranged from 125 ms to 7 s. They demonstrated orientation-specific fMRI adaptation in areas V3 and V4 /7/. They did not perform an explicit statistical test to reveal differences of fMRI-adaptation effects with respect to repetition lag. However, there is evidence (Figure 5 of ref. /7/) that they observed the effect across all repetition delays.

Huettel *et al.* /39/ studied direction-selective fMRI-adaptation effects using six ISIs between 1 s and 6 s. They found clear fMRI-adaptation effects in lateral temporal-occipital and peri-calcarine cortex for repeated gratings moving in the same direction in contrast to gratings moving in opposite directions for all delays. Direction-selective fMRI adaptation was strongest with short ISIs.

Murray *et al.* /71/ presented arrays of broadband elements (disks that were half black and half white), in which elements were repeated either at the same or a different position. Using two different ISIs of 100 ms and 800 ms they investigated the effect of repetition delay on spatially-specific fMRI adaptation. They observed significant fMRI-adaptation effects for the repetition of the exact array (without a position change of the elements) in early visual areas V1, V2 and V3 for both ISIs. No area showed a significant effect of ISI.

Intermediate repetition delays (8 s - minutes, but within a single scanning session)

Henson *et al.* /32/ used an event-related design with intermixed presentation. They presented familiar and unfamiliar faces and symbols and the repetition lag ranged from 8 s to 20 min (1 to 147 intervening stimuli, median 45). They identified a right fusiform region that showed a significant interaction between familiarity and repetition lag for both faces and symbols: The response to the repetition of a familiar stimulus increased with lag while the response to the repetition of an unfamiliar stimulus decreased /32/. The authors concluded that the processes that underlie the observed repetition effects in fusiform cortex decay over minutes.

Long repetition delays (hours, days)

Van Turennout and co-workers /100/ investigated intermediate (30 s) and long-lag (3 days) repetition delays. They found fMRI-adaptation effects for intermediate and long repetition delays for both nameable and nonsense objects in the occipitotemporal cortex. They also found fMRI-adaptation effects for both repetition delays in the inferior frontal cortex but only for nameable objects. Interestingly, the adaptation was strongest in occipitotemporal areas for the intermediate repetition delay and in frontal regions for the long repetition delay /100/. In a second study, van Turennout and colleagues /101/ further investigated the temporal evolution of those repetition effects, this time applying three different long repetition lags (1 h, 6 h, and 3 days). Van Turennout *et al.* introduced the number of repetitions as another independent variable. They were thus able to investigate interaction effects between repetition lag and number of repetitions /101/. Again, fMRI-adaptation effects were observable in occipitotemporal regions as well as in frontal cortex. There was no interaction effect between repetition time and number of repetitions in occipitotemporal regions: the fMRI signal decreased with number of repetitions, but the amount of fMRI adaptation to repeated objects was the same across the three long repetition lags. In contrast, in left inferior frontal cortex, multiple exposures led to a larger fMRI-adaptation effect only with long repetition lags /101/. These results point towards two possibly different adaptation effects in visual and frontal cortex. In sum, van Turennout *et al.* /100,101/ showed that fMRI-adaptation effects in occipitotemporal cortex favor intermediate repetition lags, but can also be reliably observed at several long lags (hours, days), and that those adaptation effects are influenced by the number of repetitions.

Mixed repetition delays

Soon *et al.* /88/ compared a short ISI of 3 s to an intermediate ISI of 6 s. They presented unfamiliar faces and found fMRI adaptation to repeated faces in fusiform cortex for both ISIs. They detected a trend for stronger fMRI adaptation for an ISI of 3 s in posterior fusiform gyrus /88/.

Henson and colleagues /36/ investigated the effect of lag on fMRI adaptation within an event-related design with intermixed presentation. They compared ISIs of 780 ms (short), 2,260 ms (short, with one intervening stimulus), 2,260 ms (short, with no intervening stimulus) and 96 s (intermediate) /36/. The main differences were found in object-selective regions in ventral occipital and temporal cortices, but also prefrontal areas: They detected fMRI-adaptation effects for repeated objects, where the size of adaptation decreased with increasing lag. Particularly, parahippocampal and lateral inferior occipital regions demonstrated a repetition-lag interaction.

We conclude that fMRI-adaptation effects in visual areas are observable even with very short delays (100 ms) and that they seem to be strongest for short or intermediate lags. In frontal areas, however, fMRI-adaptation effects occur also with very long repetition lags. Again, as in the case of the experimental design, we conclude that by using different repetition lags one might tap into different neuronal adaptation effects in a single brain area, and that the relationship between fMRI-adaptation effects and repetition lag varies substantially across brain regions. However, most importantly, it seems that fMRI adaptation is able to detect various repetition effects across large time scales.

Stimulus duration

As described above, the duration of the adaptor stimulus has a high impact on orientation-selective fMRI-adaptation effects in primary visual areas when comparing different experimental designs. However, to our knowledge only one article investigated the influence of stimulus duration on fMRI-adaptation effects directly. Zago and colleagues /113/ presented familiar everyday objects for 40 to 1,900 ms followed by a mask of 1,960 to 100 ms. The test stimulus was then presented for 500 ms. fMRI-adaptation effects in object-related visual regions increased with increasing stimulus duration, peaking at 250 ms, and decreased with longer exposures. These results may reflect different neuronal adaptation effects for short versus long stimulus durations. Unfortunately, the findings are confounded with varying repetition lags (as can be seen in the presentation durations of the mask),

that is, the shorter the stimulus duration of the adaptor stimulus, the longer the mask and thus, the longer the repetition lag. Thus based on this study a clear-cut interpretation of the influence of stimulus duration on adaptation is not possible.

Number of repetitions

Sayres and Grill-Spector /82/ demonstrated that fMRI-adaptation effects increased with the number of successive repetitions reaching a plateau at five repetitions. They tested up to eight repetitions of animal pictures and found this effect in LOC. Reber *et al.* /78/ found fMRI-adaptation effects to the second presentation (repetition) in a number of brain regions that displayed no further reduction with the following repetitions. Only some regions in the right fusiform gyrus and inferior temporal lobe exhibited linearly increasing fMRI adaptation responses for the second to the eighth presentation. A study by van Turennout and colleagues /101/ also found increasing fMRI adaptation with increasing number of repetitions in ventral visual cortex. In summary, brain regions in the ventral visual pathway seem to exhibit increasing fMRI-adaptation effects with increasing number of repetitions, while other brain regions do not show further adaptation beyond the first repetition. This is a further hint that the underlying adaptation mechanisms might differ across brain regions.

VISIBILITY/AWARENESS

There is evidence that repetition priming can occur without conscious perception of the primes /96/. On the other hand, recent psychophysical experiments on low-level vision have suggested that certain types of adaptation depend on awareness of the presented stimuli /5/. This section is devoted to studies that manipulated the visibility of the adaptor stimulus, the test stimulus, or both, and looked for consequences on the fMRI-adaptation effect to repeated stimuli. Furthermore, we also report on studies that used illusory stimuli to see whether they also elicit fMRI adaptation.

Using a combination of forward and backward masking, Eddy and co-workers /15/ investigated fMRI-adaptation effects to invisible stimuli. In a

classic event-related design they presented two objects, where the adaptor image was preceded and followed by a masking stimulus. Stimulus presentation times were short. Eddy *et al.* found fMRI-adaptation effects for repeated identical objects in several visual areas (fusiform gyrus, occipito-temporal regions). Furthermore, a region of the posterior inferotemporal gyrus even showed an fMRI-adaptation effect for repeated exemplar objects (two different cats). The authors conclude that areas of the ventral pathway are sensitive to image repetitions even when the adaptor stimulus is effectively masked.

Using an event-related design with pre-adaptation block, James and Gauthier /45/ investigated fMRI-adaptation effects for masked stimuli. They first presented object stimuli at full contrast in a localizer experiment (pre-adaptation block). Several minutes later those objects were repeated (among new objects) within an event-related scan. This time, object stimuli were shown at three different levels of contrast embedded in random noise with backward masking. James and Gauthier found fMRI-adaptation effects to repeated objects only when subjects reported having been successful in identifying those objects /45/. In contrast, they found an enhanced signal to repeated objects that could not be identified by the subjects.

Turk-Browne and colleagues /97/ manipulated the contrast of scene stimuli in a slow event-related design. They found fMRI-adaptation effects for the repetition of identical high-contrast scenes in comparison to different high-contrast scenes in the parahippocampal place area. Furthermore, they found fMRI enhancement for the repetition of identical low-contrast scenes in comparison to different low-contrast scenes in the same area /97/.

In summary, Eddy *et al.* /15/ convincingly demonstrated that stimuli that are presented, but not perceived (due to effective masking) produce fMRI-adaptation effects in the LOC. A few studies investigated the inverse phenomenon: visual illusions, in which stimuli are perceived, but not presented. Montaser-Kouhsari *et al.* demonstrated fMRI-adaptation effects to illusory lines in early as well as late visual areas /68,105/. In our own study we report on a cortical network of areas showing fMRI-adaptation to illusory, rotating objects /106/.

Furthermore, we also demonstrate fMRI-adaptation effects to perceptually completed shapes in the ventral visual cortex /104/.

Thus, both stimuli that are not perceived although presented and stimuli that are perceived although not presented can lead to fMRI-adaptation effects. However, as soon as stimuli are degraded in contrast, as tested by James and Gauthier /45/ and Turk-Browne and colleagues /97/, those stimuli elicit fMRI enhancements in the respective areas. Since both later studies also used masking procedures, it is not clear how this might have affected the degradation of the stimuli. A possible explanation for these results is that repetition-related decreases occur if the first stimulus can be successfully processed by the visual system (that does not necessarily involve conscious perception). As soon as the first stimulus is not identifiable (due to degradation), the repetition of this stimulus might however support recognition. This extra processing that eventually leads to recognition is reflected in the repetition enhancement.

ATTENTION

Attention enhances the efficiency of stimulus processing. Studies have shown that this effect is subserved by an enhanced selectivity of the neuronal population representing that stimulus /89/. Since adaptation can be seen as a marker for sensitivity/selectivity, there should be a direct influence of attention on the amount of adaptation.

The first study that investigated the influence of attention on fMRI adaptation was conducted by Murray and Wojciulik /70/. Based on well-established fMRI-adaptation effects to shapes in the LÖC the authors presented novel objects to their subjects during scanning. In a classic event-related design, one object could be followed either by a completely identical stimulus or by a stimulus identical in shape but rotated in plane. Attention was manipulated by instructing the subjects either to perform a task on the objects or a task on the fixation dot. Murray and Wojciulik observed a significant effect of rotation with decreasing amounts of adaption for increasing rotation angles in the LOC. Most importantly, they found a

significant task-by-rotation interaction, indicating that attention to the objects in comparison to attention to the fixation point enhances the rotation-dependent selectivity /70/. In our own study /106/ we employed a similar attentional manipulation to that of Murray and Wojciulik. We found that fMRI-adaptation effects to illusory objects can only be observed if subjects are engaged in tasks that draw their attention towards the objects. A demanding center task abolished fMRI-adaptation effects in a network of cortical areas. However, it is hard to tell whether those effects found by Murray and Wojciulik and us rest upon spatial attention (attending to the complete object or attending to the small fixation spot) or object-based attention, because the manipulation of attention is confounded by the use of two completely different tasks.

Spatial attention

Eger and colleagues tested the effect of spatial attention on fMRI adaptation /16/. They presented different objects to the left and the right of the fixation cross, followed by a single object at the center of the screen that could be an identical repetition of one of the first objects or a mirror image of one of the first objects. The modulation of spatial attention was achieved by instructing subjects to attend to either the left or the right side (while keeping central fixation). Eger *et al.* found that only attended objects produced reliable fMRI-adaptation effects in lateral occipital and fusiform regions /16/. Further confirmation that fMRI adaptation in ventral visual cortex is strongly dependent on spatial attention to the stimulus comes from a study by Henson and Mouchlianitis /37/. They showed subjects face and house stimuli on the left and right side of fixation and instructed them to attend either left or right. Again, reliable fMRI-adaptation effects were only found for stimuli that were attended. Moreover, those effects were category-specific in the sense that they were exclusively found for faces in the fusiform face area (FFA) and for houses in the parahippocampal place area (PPA) /37/.

Object-based attention

Apart from this strong influence of spatial attention on fMRI-adaptation effects, the influence of object-based attention was studied as well in two elegant papers by Yi and colleagues /111,112/. Both studies made use of overlapping scene and face stimuli that were created by flickering a scene and a face image at a very high rate (the flicker itself was perceptually not resolvable). During scanning, subjects were asked to attend either to the scenes alone or to faces alone. In the PPA, fMRI-adaptation effects occurred only for attended repeated scenes, but not for ignored repeated scenes or attended repeated faces /111,112/. In the FFA, fMRI-adaptation effects occurred only for attended repeated faces, but not for ignored repeated faces or attended repeated scenes /111/. Interestingly, two different experimental designs were used: in their first experiment, Yi and Chun employed an event-related design with intermixed presentation /111/, while in the second experimental series they made use of a block design with different numbers of repetitions. The effect of object-based attention was the same across experimental designs. A similar approach in a study of object-based attention was taken by Vuilleumier *et al.* /103/. Again, overlapping stimuli were created. Attended repeated objects elicited fMRI-adaptation effects in various occipitotemporal brain regions as well as in frontal cortex.

Attention effects on fMRI adaptation in early visual areas

Interestingly, most studies that searched for fMRI-adaptation effects in early visual areas, especially primary visual cortex, used demanding center tasks to draw subjects' attention to the center of the screen (to prevent eye movements). With the appropriate experimental design involving longer pre-adaptation phases, orientation-dependent fMRI-adaptation effects were observable in V1 /24,48, 60,68/ although subjects did not explicitly attend the oriented stimuli. In a recent experiment, Liu *et al.*, however, investigated the influence of feature-based attention on orientation-selective fMRI adaptation in human primary visual cortex in more detail /62/. They used composite stimuli: a double

grating composed of two differently oriented gratings. Subjects were instructed to attend to one grating/one orientation only. In every area that they investigated (V1, V2, V3, hV4, LO1, LO2, V3A/B, V7), Liu *et al.* found an orientation-dependent fMRI-adaptation effect for the attended grating in contrast to the unattended grating /62/. Interestingly, they computed correlation coefficients between behavioral measures of orientation-dependent adaptation (tilt after-effect) with the attentional effect on the fMRI-adaptation signal for every visual area and found that there was a significant correlation only for area V1. Liu *et al.* speculate that if attention selectively modulates the response of neurons representing specific features, then the most efficient modulation would occur on the level in which neurons show the highest functional specialization for this feature (in this case in V1 for orientation). We can summarize that orientation-dependent fMRI-adaptation effects in early visual cortex can be observed without attention being directed towards the stimuli, but that if attention is directed to the stimulus, this enhances the fMRI-adaptation effect.

Additional evidence that fMRI-adaptation effects in early visual areas are observable independent of the attentional focus comes from a study by Murray and colleagues /71/. Testing spatially specific adaptation - that is adaptation to retinotopic position - Murray and colleagues did not find any differences for V1 whether or not the stimuli were attended. They used sparsely distributed, oriented black-and-white disks in a classic event-related design. A stimulus array was followed either by the identical array or by a different array in which individual elements were displaced by 1 degree. Subjects performed either a same/different task on the two stimulus arrays or a demanding center task. Spatially-specific fMRI-adaptation effects for the identical array were observed in early visual areas V1, V2 and V3, independent of the task being performed /71/.

We conclude that fMRI-adaptation effects in higher visual areas seem to be highly susceptible to attentional modulation. fMRI-adaptation effects in early visual areas are less dependent on the attentional focus, i.e., they are also observable without attention.

COMPARING fMRI AND NEURAL ADAPTATION

In conclusion, fMRI-adaptation effects can be reliably elicited with various experimental designs. However, there seem to be differences whether a certain design will reveal adaptation effects across brain regions in general, across visual areas in particular, and even within a visual area across neuronal subpopulations coding for different visual features. We therefore hypothesize that the observed fMRI-adaptation effects reflect various neuronal adaptation mechanisms dependent on the experimental design and the stimulation parameters employed. That there are indeed various adaptation mechanisms at the level of single neurons or cell assemblies has been shown /51/.

Still, one might argue that in the case of neuroimaging the observed differences between experimental designs do not reflect differences in the neural mechanisms, but are attributable to non-linear effects, e.g., in neurovascular coupling /7,38/. However, two electrophysiological studies support the idea that the use of different experimental designs also has a strong impact on the neuronal adaptive mechanisms. Priebe and colleagues /75, 76/ and Kohn and Movshon /49/ addressed the question whether adaptation of cells in the motion-sensitive region (MT) of the macaque might be inherited from primary visual cortex. They adapted one portion of the receptive field of an MT neuron and assessed the transfer of adaptation to another portion of the receptive field. A transfer of adaptation from one location to the other would speak in favor of an adaptation mechanism that has to be intrinsically computed in MT or signalled via feedback from higher areas, while no transfer of adaptation would indicate that the effects were based on input from early visual areas. Surprisingly, Priebe and colleagues /75/ found a transfer of adaptation, while Kohn and Movshon did not /49/. The discrepant results are most likely caused by the use of different adaptation approaches. Priebe *et al.* /75/ used brief presentations of stimuli (64 ms stimulus durations and ISIs ranging from 0 to 256 ms), while Kohn and Movshon /49/ investigated adaptation effects that occurred after prolonged stimulation (pre-adaptation phase of 40 s plus top-up adaptors of 5 s). Furthermore, the two studies differed also in their stimulus material: Priebe *et al.*

/75/ used random dots while Kohn and Movshon /49/ used sine-wave gratings. We therefore conclude that differences in experimental design and/or stimulus material might reveal different neuronal adaptation mechanisms. How these mechanisms relate to each other and how they are generated in the cell or cell assemblies remains to be answered. Furthermore, the question whether adaptation in higher visual areas might be inherited from earlier visual areas or might be modulated by other areas is still open. Importantly, the fact that different experimental designs lead to different adaptation effects at the neuronal level might be used as evidence that the observed differences at the hemodynamic level indeed reflect neuronal differences.

In contrast, a study by Sawamura and coworkers /81/ investigated neuronal adaptation mechanisms with two different approaches and found no difference between the designs. Interestingly, this research group employed experimental designs derived from typical fMRI adaptation studies. They used a classic event-related design and a block design with different numbers of repetitions. Sawamura *et al.* studied the repetition-related activity of IT cells in macaque monkeys; stimuli comprised different familiar objects. Most importantly, they did not find any differences between the two experimental designs; both approaches reliably elicited neuronal adaptation to the repetition of objects in IT cells /81/. Thus, it seems that prolonged adaptation phases, as used by Kohn and Movshon /49/, are a special case and might involve different mechanisms from short-lag adaptation.

Further support for this hypothesis stems from two different lines of evidence: First, it has been shown that prolonged adaptation does not only influence firing rates, but also the tuning of neurons. Kohn and Movshon /50/ studied the direction tuning of cells in areas MT and V1 of the macaque and found that adaptation of near-preferred direction caused a tuning shift toward the adapted direction for MT cells but not for V1 cells /50/. Furthermore, this 'attractive' shift of MT cells stands in direct contrast to the 'repulsive' shift of V1 cells that has been observed, e.g., for orientation /14,69/. Beyond showing that prolonged adaptation has a major impact on a cell's tuning curves, this

study also indicates that different cortical regions may adapt to repetitive input in distinct ways. Second, Tolias and coworkers found that long adaptation periods lead to strong direction-selective adaptation in V4v of the macaque - an area that is normally not seen to comprise cells that are strongly direction-selective /94/. This finding is in line with the results by Fang *et al.* /24/ and Epstein *et al.* /22/ reviewed above.

In summary, prolonged adaptation targets both early and late visual cortex and has a strong influence not only on firing rates but also on the tuning of cells. We hypothesize that some of the effects observed during prolonged adaptation in higher visual areas are inherited from early visual areas. In contrast, short-lag adaptation effects can be detected with much more ease in higher visual areas. We hypothesize that these short-lag adaptation effects mark an intrinsic adaptive behavior of cells within a cortical region or may be elicited by feedback connections /66,76/. We therefore argue that fMRI adaptation does not refer to a single process but rather to a number of possible neuronal adaptation mechanisms.

Finally, we want to emphasize the difficulty of interpreting null effects in fMRI-adaptation designs. Based on our current findings on the impact of experimental design, stimulus duration, repetition lag, visibility, and attention, null effects in fMRI adaptation studies might be due to numerous factors and their interactions, and are thus not easily interpretable. Further empirical evidence is needed to gain a complete picture of the different effects of stimulus repetition on the population and neuronal level.

FUNCTIONAL ROLE OF ADAPTATION

A fundamental and still open question is the functional role of adaptation. In what follows we discuss three possible roles of adaptation: 1. adaptation being the neuronal correlate of behavioral priming, 2. adaptation enhancing stimulus selectivity, and 3. adaptation mediating memory formation.

fMRI adaptation was first thought to be the neuronal correlate of behavioral priming, since a

number of studies investigating behavioral priming phenomena found fMRI adaptation in parallel with reaction-time facilitation /9,34,35,64,72,83,84/. However, some recent studies showed a dissociation between behavioral priming and fMRI-adaptation effects /10,27,82,110/. Thus, the concept of adaptation as the neuronal correlate of behavioral priming has been challenged. Furthermore, using transcranial magnetic stimulation (TMS), Wig *et al.* /108/ showed that behavioral priming was absent and that fMRI-adaptation effects in frontal cortex but not in ventral visual areas were abolished, when TMS was applied to the frontal cortex /108/. Those studies point towards a more complex picture of the relationship between behavioral priming and fMRI adaptation such that fMRI adaptation in visual areas does not necessarily reflect behavioral priming, but possibly fMRI adaptation in frontal cortex does /85/.

Secondly, adaptation has been claimed to enhance stimulus selectivity /94/. In this respect, a recent study by Sawamura and colleagues /81/ is of great importance. Neurons in IT cortex of the macaque were recorded in a single-cell study. Sawamura *et al.* selected two stimuli (A and B) to which the neuron responded equally well (with the same high amount of spiking) and other stimuli to which the neuron responded weakly (C). Those stimuli were tested in an adaptation experiment. The main finding of Sawamura and coworkers was that the repetition of the same stimulus (A-A) always elicited a stronger adaptation than the presentation of A-B or B-A, although the initial responses were the same for A and B /81/. In other words, stimulus selectivity based on adaptation was much stronger than the selectivity based on the initial response of the neuron to the stimulus. This finding was independent of the experimental design employed. Further support for adaptation-dependent selectivity stems from the work of Tolias *et al.* /93,94/. Based on their neuroimaging and electrophysiological investigations, Tolias and coworkers propose that adaptation may finally increase the sensitivity of neurons to detect changes in the environment.

A third functional role of adaptation was recently proposed on the basis of a neuropsychological case study. Williams and coworkers examined a rare

case of developmental prosopamnesia /109/. The patient reported a lifelong difficulty in recognizing people by their faces, and extensive behavioral testing revealed that the patient is severely impaired in memorizing unfamiliar faces and relies on a feature-matching strategy when judging facial identity. However, the patient was able to develop familiarization with faces over months (e.g., famous faces and faces of family members) and her discrimination between familiar and unfamiliar faces was very good /109/. Williams and colleagues employed an event-related adaptation design with intermixed presentation to study the functioning of the patient's fusiform face area. They presented familiar and unfamiliar faces and places while the patient was instructed to passively view the images. fMRI adaptation to the repetition of familiar and unfamiliar places was observed in PPA (both in the patient and in a group of control subjects). Most interestingly, the right FFA displayed fMRI adaptation to familiar faces but not to unfamiliar faces in the patient, while both familiar and unfamiliar faces caused adaptation in control subjects /109/. The authors conclude that repetition suppression has revealed a neuronal marker for the striking deficit in this case of prosopamnesia.

Further evidence comes from studies of elderly patients who suffer from cognitive impairments. Focusing on the hippocampus and parahippocampal gyri, Johnson *et al.* /47/ found clear fMRI-adaptation effects for repeated faces in a group of cognitively healthy, old subjects. However, no adaptation effect could be observed in the patients. A study by Lustig and Buckner did not find any evidence for impaired fMRI adaptation in a group of patients in an early stage of amnesia /63/.

We conclude that further empirical evidence is needed to understand the phenomenon of adaptation. Since the phenomenon itself occurs at various levels - behavioral, cellular, network - a multi-method approach is highly desirable /11/. Interference studies using TMS /108/ and neuropsychological case studies /109/, but also pharmacological approaches /4,91,92/, might reveal a more detailed picture of the underlying mechanisms of adaptation in humans. The field of adaptation research will definitely profit from the combination of electrophysiological and neuroimaging techniques devoted

to unravel the mechanisms of neurovascular coupling. This will increase the reliability, explanatory power, and the predictive validity of fMRI adaptation.

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