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Review

Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI)

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Abstract

Functional magnetic resonance imaging (fMRI) measures the blood oxygen level-dependent (BOLD) signal related to neuronal activity. So far, this technique has been limited by time-consuming data analysis impeding on-line analysis. In particular, no brain–computer interface (BCI) was available which provided on-line feedback to learn physiological self-regulation of the BOLD signal. Recently, studies have shown that fMRI feedback is feasible and facilitates voluntary control of brain activity. Here we review these studies to make the fMRI feedback methodology accessible to a broader scientific community such as researchers concerned with functional brain imaging and the neurobiology of learning. Methodological and conceptual limitations were substantially reduced by artefact control, sensitivity improvements, real-time algorithms, and adapted experimental designs. Physiological self-regulation of the local BOLD response is a new paradigm for cognitive neuroscience to study brain plasticity and the functional relevance of regulated brain areas by modification of behaviour. Voluntary control of abnormal activity in circumscribed brain areas may even be applied as psychophysiological treatment.
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Keywords: Real-time functional magnetic resonance imaging; Brain–computer interface; Neurofeedback; Operant conditioning; Physiological self-regulation; Review

Abbreviations: ACC, Anterior cingulate cortex; BCI, Brain–computer interface; BOLD, Blood oxygen level-dependent; CNR, Contrast-to-noise ratio; EEG, Electroencephalography; EPI, Echo-planar imaging; fMRI, Functional magnetic resonance imaging; M1, Primary motor cortex; PPA, Parahippocampal place area; ROI, Region of interest; S1, Primary somatosensory cortex; SCP, Slow cortical potential; SMA, Supplementary motor area; SNR, Signal-to-noise ratio.

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1. Introduction

Over the last three decades, different types of brain–computer interfaces (BCI) have been developed on the basis of electrophysiological recordings. These BCIs allow for on-line measurement of brain activity and are used in different applications, such as communication and control [6,23,63,94]. Only recently with the advent of high performance magnetic resonance scanners and computers, a novel type of BCI based on non-invasive functional magnetic resonance imaging (fMRI) became available. Although few studies have been reported so far [20,69,92,93,95,97], there is clear evidence that human subjects can use these BCIs to learn self-regulation of activity in circumscribed brain regions. Self-regulation of the fMRI signal offers new ways to study the relation between behaviour, brain function, and *local* brain activity. An increasing number of research groups are working in this field and we expect the area of research to develop rapidly. By discussing the current studies, this review will provide the reader with the basic principles of fMRI neurofeedback and may serve as a guideline to future studies. Real-time fMRI and neurofeedback relies on specific methodological advances and experimental strategies which are commonly not described in detail. Summarizing the technical aspects and general experimental procedure, we want to encourage the reader to get further interested in fMRI-BCIs.

In the following, we will introduce the concept of on-line feedback of electrophysiological signals (Section 1.1). Learning to regulate fMRI signals will be discussed afterwards, including an overview of the current research (Section 1.2). Then, we will systematically review the technology (Section 2) and operant learning in fMRI feedback studies (Section 3). Finally, we will outline the main findings and possible future developments with main emphasis on techniques and possible applications (Section 4).

1.1. Self-regulation and its behavioural effects

In neurofeedback studies using electroencephalography (EEG), healthy subjects and patients learned to control electric brain activity by operant training with feedback of specific EEG components as reward (for operant training, see Section 3). Learned regulation of slow cortical EEG potentials (SCP; cortical potentials changing with frequencies <1 Hz) was applied for communication in severely paralyzed patients [6,48] and suppression of epileptic activity [46]. Self-regulated oscillatory EEG activity could control a hand prosthesis [66] and support communication [62] in patients with severe motor impairments.

In addition to communication and control with brain signals, neurofeedback is an interesting experimental approach in cognitive neuroscience. Conventionally, studies treat brain activity as a variable which is *dependent* on the effect of stimulation or behaviour, e.g., they assess effects of visual, auditory or other stimuli, or executed movements on brain activity [59]. In contrast, neurofeedback experiments use self-regulated brain activity as the *independent* variable. Thus, we can study effects of voluntarily controlled brain activity on behaviour. Self-regulation of SCP or oscillatory EEG signals has yielded various behavioural effects: decreased reaction times in a motor task [76], faster lexical decisions [74], altered emotional responses [1], and enhanced musical performance [24] in healthy subjects. In patients, self-regulation of brain activity was applied to treat symptoms of attention-deficit/hyperactivity disorder (ADHD; [29]) and to suppress epileptic activity, i.e., 12 weeks of feedback training were shown to be effective in a one year follow-up [46].

Many of these effects were dependent on location and function of the regulated brain structure. For example, differential reaction times of the right and the left hand varied in a motor task depending on the hemispheric asymmetry of the self-regulated SCP [76]. Responses in a lexical decision task were faster during self-regulated negative shifts of the SCP at the left-hemispheric language cortices as compared to positive shifts [74]. Emotional responses were dependent on the asymmetry of frontal alpha activity (oscillatory EEG activity at ≈10 Hz; [1]). Such specific behavioural effects may help to explore the function of the respective brain regions.

1.2. Self-regulation using real-time fMRI

The previous EEG neurofeedback studies were limited with respect to spatial specificity and the choice of brain regions. The EEG offers only low spatial resolution and ambiguous allocation of neuronal activity, because the underlying electric sources have to be reconstructed from the distribution of electric potentials across the scalp. Electrical activity is attenuated by the electrical resistance of the skull and skin layers. Hence, spatial patterns of EEG activity may be blurred with reduced amplitudes, impairing precise localisation and spatial specificity.

Functional MRI, in contrast, allows for non-invasive recording of activity across the entire brain with high spatial resolution in the range of millimetres (for reviews, see [37,51,59]). Functional MRI measures the blood oxygen level-dependent (BOLD) response, i.e., signal differences due to local changes in the concentration of deoxygenated haemoglobin in the brain tissue which depends on neuronal metabolism and activity. The maximal change of the BOLD signal in response to neural activity is delayed by approx. 6 s. Despite being an indirect measure, there is increasing evidence for a strong correlation between the BOLD signal and electric brain activity, in particular local field potentials (LFP; for a review, see [51]). Studies combining fMRI with EEG showed correlations between the amplitude and localisation of the electric generators and localised BOLD signal changes [4,5]. Hence, non-invasive fMRI promises new possibilities for the regulation of local brain activity and for studies on behavioural consequences of self-modulated activity.

Until recently, most fMRI setups did not allow for online analysis, and the majority of fMRI studies still perform off-line data analysis. Recent advances in acquisition techniques [68,72], computational power [33], and algorithms [15,16,25,31,34,56,81,89] increased functional sensitivity and speed of fMRI considerably, making real-time applications feasible. Few experiments were reported which applied operant training of the BOLD-response using real-time fMRI and feedback [20,69,92,93,95,97].

The feedback studies targeted different cortical and subcortical areas (for an overview of the studies, see Table 1; for anatomical locations and technical setup, see Figs. 1 and 2): the sensorimotor cortex [20,95,97], supplementary motor area (SMA; [92]), posterior aspect of superior temporal gyrus [95], medial superior frontal gyrus [95], parahippocampal place area (PPA; [92]), the anterior cingulate cortex (ACC; [93,95]), and the amygdala [69].

For an overview, we describe the experiments briefly in chronological order:

Yoo and Jolesz [97] investigated whether subjects could adjust their task performance based on fMRI feedback such that the extent of the activation in the sensorimotor area increased. Subjects ($n = 5$) performed right hand movements in a block design (alternating 15 s rest/15 s movement) and were presented statistical maps of brain activations following a rest-task period (after ≈60 s; for an exemplary statistical map, see Fig. 3a). Starting from single digit movements as a reference, the subjects recruited more hand-muscle groups to activate larger cortical areas. This indicated an adjustment of the task strategy due to the visual feedback.

Posse et al. [69] measured BOLD responses in the amygdala during trials of self-induced sadness (20 s rest/30 s self-induced sadness or neutral mood). The experimenter rated the functional maps and provided the subject with verbal feedback of the signal change in the amygdala after each trial. Subjects ($n = 6$) achieved significant differences in the activity of the amygdala between the sad and neutral

Table 1
Studies on self-regulation of the BOLD signal using real-time fMRI[a]

Study	Target region (ROI) and definition	Feedback and design	Prior instructions, participants	Delay	Results: control, learning, strategies, behaviour	Imaging and on-line analysis techniques	Number of subjects
Yoo and Jolesz (2002; [97])	M1, S1, parts of pre-motor areas; anatomical	Functional map; activation should be expanded modifying a hand motor task (15 s rest/15 s movement)	Explanation of functional map; fMRI-naïve	60 s	Successful adjustment of motor behaviour, i.e., use of more muscle groups to extend the activation	1.5 T, EPI, no preprocessing, thresholded difference maps (*t*-test)	5
Posse et al. (2003; [69])	Amygdala; anatomical	Verbal feedback of activation as rated by experimenter; self-induced sadness and neutral mood triggered by sad and neutral face (20 s rest/30 s mood induction)	Guideline for mood induction; no information on background of participants	60 s	Activations correlated with subject's ratings of negative mood, significant difference in activation between neutral and sad trials, learning effects were not assessed	1.5 T, mEPI, compensation of signal dropouts, motion correction, spatial smoothing, sliding window correlation	6
Weiskopf et al. (2003; [93])	ACcd, ACad; anatomical	Two curves of activity in ACcd, ACad; increasing both curves (60 s rest/ 60 s increase)	Neuroscience background; member of the research group	<2 s	Control of both ROIs, increase of control in ACad, changes in arousal and valence	1.5 T, EPI, motion correction, GLM, rectangular ROIs	1
deCharms et al. (2004; [20])	M1, S1; functional localiser	Three curves: activity of (1) ROI, (2) background, and (3) ROI minus background; imagined hand movement and increase of ROI curve (30 s rest/30 s increase); control group with pseudo-feedback, level of required activity adapted to success of regulation	Training of imagined and executed hand movement (1 h), volunteers including one member of the research group	<2 s	Local increase of activity in ROI across training, successful regulation also in the absence of feedback in post-training session; no effect in control group	3 T, spiral acquisition, bite bar for immobilisation, difference maps, rectangular ROIs, electromyography	6 subjects/ 3 controls
Weiskopf et al. (2004; [92])	SMA, PPA; functional localiser	One curve of differential activity in SMA and PPA; up-/down-regulation of curve (50 s up-/50 s down-regulation/ 31 s rest)	Motor and visual imagery as initial strategy; 1 fMRI-naïve, three members of the research group	<1.3 s	Successful differential and bidirectional regulation, increase of control in two subjects	3 T, mEPI, distortion and motion correction, GLM with two regressors, rectangular ROIs	4
Yoo et al. (2004; [95])	M1, medial superior frontal gyrus, left Broca's area, auditory association areas; functional localiser	Emphasis on communication and control using the BOLD signal and not on neurofeedback; classified brain activity was used to navigate through a maze	Practicing of mental tasks to generate spatially distinct template fMRI maps	120 s	Successful generation of specific brain activity patterns to generate cursor commands used for navigating through a maze	3 T, EPI, thresholded difference maps (*t*-test), template matching to extract four different cursor movements	3

[a] Abbreviations used in the table in alphabetical order: ACC = anterior cingulate cortex; ACad = rostral-ventral ACC, affective division; ACcd = dorsal ACC, cognitive division; BOLD = blood oxygen level-dependent; EPI = echo-planar imaging; fMRI = functional magnetic resonance imaging; GLM = general linear model; M1 = primary motor cortex; mEPI = single-shot multi-echo EPI; PPA = parahippocampal place area; ROI = region of interest; S1 = primary somatosensory cortex; SMA = supplementary motor area.

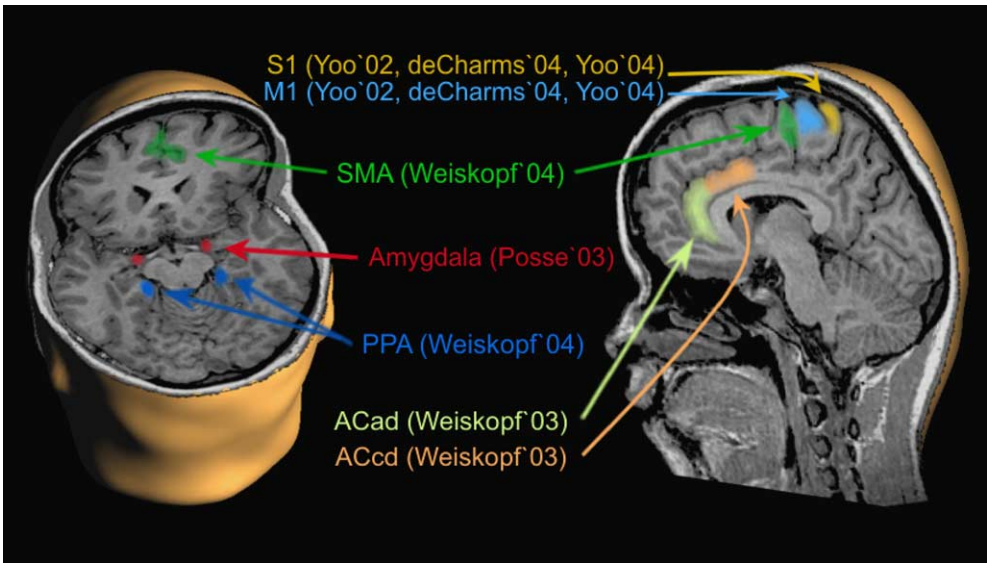

Fig. 1. Regions of interest studied with fMRI neurofeedback. Studies investigated self-regulation in the primary motor (M1), somatosensory (S1) cortex [20,95,97], left Broca's area together with the auditory association areas which are related to speech generation (not shown; [95]) and the parahippocampal place area (PPA) which is known to process visual information [92]. Moreover, higher cognitive areas such as the affective/cognitive (ACad/ACcd) subdivision of the anterior cingulate cortex (ACC; [93]), the medial superior frontal gyrus which is activated by mental calculation (not shown; [95]) and the amygdala (Amygdala [69]) involved in affective processing were chosen as target regions.

conditions and self-ratings of their mood were correlated with levels of activity. Whether regulation was achieved by learned self-regulation could not be assessed, because the feedback signal and the mood induction task were always presented together. Therefore, amygdala activation caused by learned self-regulation could not be differentiated from activation solely due to the mood induction. This study did not assess potential learning effects, e.g., at the level of self-regulated activity or self-ratings of mood.

Weiskopf et al. [93] introduced the concept of immediate feedback of the BOLD signal (delay <2 s) similar to the immediate feedback used in EEG neurofeedback. In this methodological study, two continuously updated curves were presented to the subject ($n = 1$) depicting the activity in two subdivisions of the ACC. During blocks of 60 s duration, both curves should be directed upwards (alternating 60 s rest/60 s up-regulation). Given that no strategy for regulating the ACC had been established, the subject was not instructed to use a particular strategy, but to develop his own. Being a member of the research group, the subject was aware of several mental imageries. He reported the use of imagery of winter landscapes, being engaged in snowboarding and social interactions during the up-regulation and attending to the feedback curve without performing any specific task during the rest blocks. An improved control of the rostral–ventral subdivision was observed through training, i.e., task related changes of the BOLD signal increased. The authors suggested learning of self-regulation as the underlying mechanism. Subsequent testing of the affective state using a non-verbal pictorial assessment (Self-Assessment Manikin; SAM; [10]) showed an increase in valence and arousal during self-induced up-regulation of the BOLD response.

deCharms et al. [20] studied whether subjects were able to control brain activity in the sensorimotor area. Prior to neurofeedback training subjects performed imagined and executed finger movements. Through three feedback training sessions, subjects ($n = 6$) should use motor imagery and the feedback to increase the BOLD signal in the sensorimotor cortex. Mean activity of the sensorimotor cortex was presented as a continuously updated scroll graph. A control group ($n = 3$) was provided with pseudo-feedback of brain activity, which was measured in a background region at an earlier time and not correlated with the task or behaviour. As compared to the controls, the subjects receiving contingent feedback specifically enhanced their control over the sensorimotor cortex and retained the control in a post-training session even in the absence of feedback.

Weiskopf et al. [92] assessed whether the BOLD signal in the SMA and the PPA could be controlled differentially. Subjects ($n = 4$) were provided with a continuously updated curve of the difference between mean brain activity in SMA and PPA (Fig. 3b). They were asked to use an individual control strategy. However, visual imagery, spatial navigation, or motor imagery served as a general starting point. They successfully regulated the curve up and down as required in a visually presented block design (50 s up-/50 s down-regulation/31 s rest). The task correlated BOLD signal changes were in accordance with a significant differential and bidirectional control of the SMA and PPA. In two subjects, differential control improved significantly across training sessions as evidenced by increasing changes of the BOLD signal.

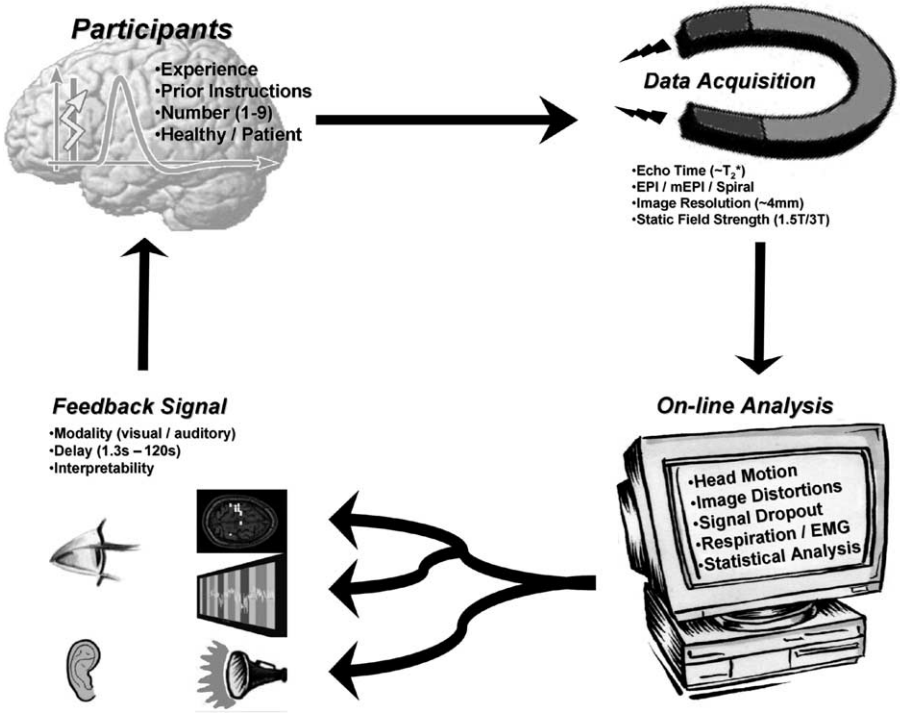

Fig. 2. Setup of an fMRI brain–computer interface (BCI) and flow of data in feedback experiments. From top left in clockwise order: *Participants:* Only healthy subjects were recruited and (in most studies) instructed to use cognitive strategies in combination with feedback to regulate local brain activity. Local brain activity was measured by fMRI using the blood oxygen level-dependent (BOLD) effect which reflects the neurovascular response to electric brain activity. The measured haemodynamic response is delayed by ≈3–6 s from the neuronal activity (see overlay). *Data acquisition:* Studies applied conventional echo-planar imaging (EPI; [93,95,97]), spiral acquisition [20] or single-shot multi-echo EPI (mEPI; [69,92]) for functional imaging. Higher field strengths (3 T; [20,92,95]) and mEPI [69,92] were used to increase the BOLD sensitivity. In-plane image resolutions of ≈4 mm were chosen as a compromise between spatial specificity and signal-to-noise ratio (SNR). *On-line analysis:* Depending on computational power and SNR, data preprocessing and analysis were performed immediately or were completed with a delay of some seconds [95,97]. Preprocessing steps varied including compensation of signal dropouts [69] and distortions [92], 3D head motion correction [69,92,93], and spatial smoothing [69]. Statistical analyses and functional maps were based on subtraction of active and rest conditions [20,95,97], correlation analysis [69] or general linear models [92,93]. In one study [95] pattern matching was added to classify four different brain states. *Feedback signal:* The types of feedback covered different modalities: verbal acoustic and visual feedback [69,95]; feedback of functional maps [97]; and feedback of continuously updated curves depicting the mean activity in target regions [20,92,93]. Depending on the paradigm and processing speed, the delay of feedback ranged from a few seconds [20,92,93] to 1 [69,97] or 2 min [95].

Yoo et al. [95] demonstrated that distributed spatial patterns of brain activity can be used to control an fMRI-BCI. In a block design, volunteers ($n = 3$) accomplished to navigate a cursor through a simple 2D maze by generating distinct fMRI activation patterns for up, down, left, and right cursor movements. To determine the cursor direction of movement, the brain activity was quantitatively compared to four reference maps that were created for each participant at the beginning of the experiment. The reference BOLD activation maps were based on four different cognitive tasks (left and right hand motor imagery, mental speech generation and mental calculation). Given that the visual feedback (successful/unsuccessful navigation through the maze) was delayed by approximately 120 s and the BCI was well calibrated to individual brain activity patterns beforehand, Yoo et al. [95] did not directly interpret the results with respect to neurofeedback. They focussed on the possibility of using real-time fMRI for communication and control, i.e., as a BCI.

2. Technical requirements

In this chapter, we will address the technical requirements of fMRI that have to be taken into account for a BCI. Operant learning of self-regulation requires contingent feedback, i.e., fast and reliable display of the brain activity (see Section 3). Thus, speed, BOLD sensitivity and artefact suppression are indispensable.

2.1. Delay of feedback

Haemodynamic coupling introduces a delay between the neuronal activation and the BOLD signal changes [59]. The onset of signal increase is delayed by ≈3 s, the peak signal change by ≈6 s. Advances in computer hardware and recent software developments reduced the additional processing delay from fMRI data acquisition to display to about 1.5 s [20,68,92,93]. A further increase of processing speed will be of limited value due to the intrinsic haemody-

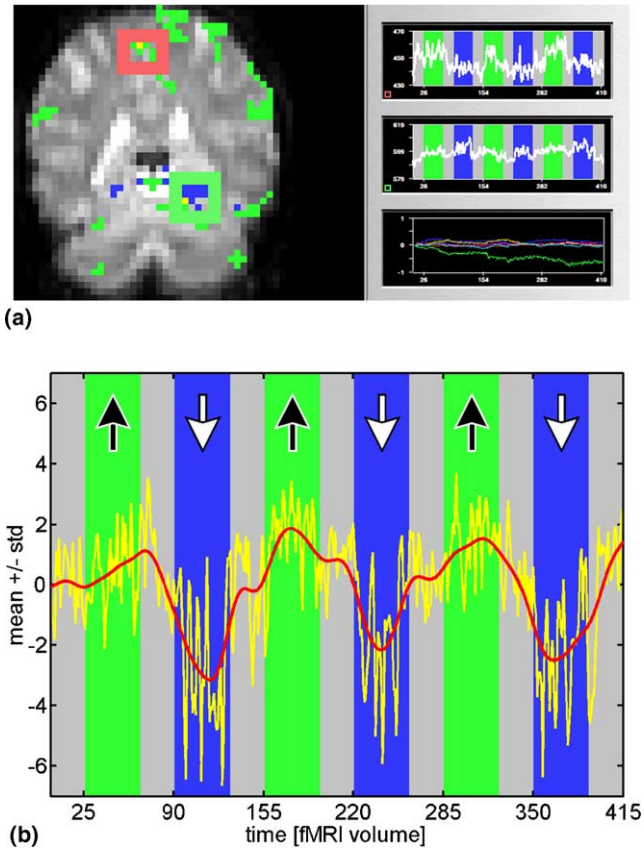

Fig. 3. Example for on-line statistical analysis and neurofeedback taken from Weiskopf et al. [92]. In this study, the subject should increase and decrease the differential feedback signal of supplementary motor area and parahippocampal place area (SMA minus PPA) according to a block design. (a) Display presented to the experimenter. On the left panel a statistical map was superimposed over one oblique echo-planar image. Green spots indicated areas which were activated during up-regulation blocks, and blue spots indicated areas which were activated during down-regulation blocks. Regions of interest were marked as rectangles which approximated the SMA (red), and PPA (green). On the right upper and middle panel time courses of SMA and PPA, respectively, were plotted as white curves superimposed over the experimental block design which was represented by grey (baseline), green (up-regulation), and blue (down-regulation) stripes. The right lower panel displayed the estimated and corrected head motion (units equal 1 mm for translations and 1° for rotations). Statistical maps and time courses were continuously updated within ~1.5 s after image acquisition. (b) Feedback screen presented to the subject. The differential BOLD signal of SMA minus PPA was presented as a continuously updated yellow curve on a colour-coded background. The tasks were presented as coloured stripes: grey indicated the baseline, during green blocks subjects had to raise the curve (up-regulation), and during blue blocks subjects had to decrease the curve (down-regulation). The red curve is the low-pass filtered (Gaussian FWHM = 25 time points) time-series. Arrows and filtered curve were not presented during on-line feedback. Mean and standard deviation were estimated from the first baseline block. (Reprinted with permission from Weiskopf et al., IEEE Transactions of Biomedical Engineering 51(6) (2004) 966–970.). © 2004 IEEE.

namic delay. In the reviewed fMRI feedback studies, delays varied from 2 min [95] to a few seconds [92,93], depending on the paradigm and computational speed.

2.2. Functional sensitivity

Higher BOLD sensitivity cannot only increase the reliability but also shortens the effective delay of the feedback, because subjects can recognise small initial signal changes earlier. Signal-to-noise ratio (SNR) and BOLD sensitivity depend on the magnetic resonance (MR) scanner and various imaging parameters. We consider only three major factors: the strength of the static magnetic field, which depends on the MR scanner and cannot be changed readily, the image resolution, and the echo time (TE). The latter two are the most important imaging parameters.

2.2.1. Strength of the static magnetic field

Thermal noise contributes to MR images of biological tissues. Either signal increase or noise reduction can improve the SNR. According to the Boltzmann-distribution magnetisation increases with the field strength. That is, more spins are in parallel with the external field, if the field strength is higher. Because the magnetisation determines the maximal signal that is measured, a theoretical signal increase proportional to the magnetic field strength should be expected, e.g., by a factor of 2 going from the clinically widely used 1.5 T [69,93,97] to the more recently applied 3 T [20,92,95]. However, in reality the gain is reduced. First, the return to maximal magnetisation after radio-frequency (RF) excitation is slower at higher field strength (due to an increased longitudinal relaxation time T_1). Thus, the magnetisation cannot be fully used unless the interval between successive image acquisitions (repetition time TR) is increased to avoid loss of signal. Second, the apparent transversal relaxation time (T_2^*) decreases at higher fields and leads to a faster decay of the MR signal. Thus, data have to be acquired faster within a shorter acquisition window which in return reduces SNR. In addition to these two effects reducing the gain in SNR for higher fields, larger distortions due to susceptibility artefacts must be considered and RF deposition increases. Currently, the range between 3 T and 4 T seems to be the most appropriate compromise between gain in SNR and emerging artefacts in fMRI [47].

2.2.2. Image resolution

Reduction of the data acquisition bandwidth reduces the contributions by thermal noise. In MR imaging, this implies a lower spatial resolution or a longer read-out time. These strategies lead to more pronounced signal dropouts or image distortions. For fast fMRI protocols, 64×64 image matrices are commonly chosen as a compromise between resolution, SNR, and distortions—resulting in 3–4 mm in-plane resolution (used in all but one reviewed study using 6 mm [69]). In post-processing, spatial filtering [69] or averaging across a region of interest (ROI; [20,92,93]) can improve SNR. Dependent on the application, the loss of spatial information can even be advantageous, e.g., to

compensate for head motion, inter-subject variability or to reduce data complexity (see Sections 2.3 and 3).

2.2.3. Echo time

More important than SNR, we must consider the CNR (contrast-to-noise ratio), i.e., the signal change due to the BOLD effect of interest as compared to other spurious signal fluctuations such as noise and artefacts. The BOLD effect depends upon the echo time (TE) which determines the time lag between the RF excitation pulse and the image sampling. For the apparent transversal relaxation time T_2^*, the expected contrast is proportional to $\mathrm{TE} \cdot \exp(-\mathrm{TE}/T_2^*)$ [21,72]. Thus, the feedback studies chose TE close to T_2^* in order to maximise functional sensitivity (about 60 ms at 1.5 T and 40 ms at 3 T).

As an advanced imaging technique, single-shot multi-echo EPI samples multiple images at different echo times as compared to one image at a single echo time. Appropriate combination of the images increases CNR without the negative effects of longer read-out times such as increased distortions [57,72,91]. To obtain images with a TE closer to T_2^* for maximal sensitivity, partial Fourier imaging technique can be used, i.e., higher spatial frequencies are only partially sampled. Hence, the low spatial frequencies of two successive images can be sampled close to T_2^* improving the main BOLD contrast. In clinical whole-body scanners at 3 T, three echo times of about 28, 43, and 73 ms can be obtained for a 64×64 matrix using 6/8 partial Fourier (or 7/8 partial Fourier using a reduced field of view in the phase-encoding direction; see [91,92]).

2.3. Artefact control

In fMRI, algorithms and filters reducing artefacts are most commonly used in off-line packages. In fMRI-BCIs, the elimination of unwanted signal changes might be even more important. Despite the limitation to fast algorithms and instantaneously available information, these procedures need to be even more robust and reliable.

2.3.1. Head motion

Movements of the head are the largest source of artefacts in fMRI. BOLD signal changes are at maximum about 5% of the image intensity and often smaller. Image contrasts, however, range from 10:1 to 100:1, leading to possibly even higher signal changes at contrast edges due to small movements as compared to BOLD signal changes. Head motions can be reduced by padding and a bite bar [20] but cannot be completely avoided. Because the head moves as a whole, rigid-body transformations are generally assumed. The six parameters in 3D-space (three for translation and three for rotation) characterizing rigid-body transformation can be estimated from the high number of volume data points (for an exemplary time-series of motion parameters, see right bottom panel in Fig. 3a).

Real-time motion correction requires robustness and speed. Large movements should not be overestimated, i.e., overcompensated, as found in current off-line evaluation packages and intensity fluctuations should not result in incorrect movement estimation [56]. Besides improving alignment of the images, motion correction might add noise and artefacts. The noise in estimated movement parameters is assessed to be about $30 \cdot x/(\sqrt{n} \cdot \mathrm{SNR})$ with spatial resolution x and number of volume elements or voxels n [56]. Therefore, Mathiak et al. [56] suggested to record at least three slices with a 64×64 image matrix to reduce the noise in movement parameters to less than 1% of the voxel size. Indeed, most feedback applications applied more slices (10–16 in [20,92,93,97]) to ensure coverage of all relevant areas even after head motion. To maintain fixed ROIs between sessions in upcoming applications, movements need to be considered which could move a ROI out of the imaged volume or deteriorate the alignment with functional navigators acquired prior to the feedback training (see Section 3.2).

2.3.2. Inhomogeneities of the static magnetic field

The different magnetic susceptibilities of bone, air, and brain tissue lead to inhomogeneities of the static magnetic field close to air–tissue interfaces like in the region of the basal brain and frontal sinuses. Because the magnetic field strength determines the frequency of the measured nuclear magnetic resonance, the inhomogeneities cause local shifts in the resonance frequencies, i.e., off-resonances.

Single-shot imaging applies one radio-frequency excitation pulse per slice. Then a read-out time (T_{RO}) of about 10–40 ms is required to encode the slice. Thus, significant local image mis-registrations occur for off-resonances approaching $1/T_{\mathrm{RO}} \approx 25$–$100$ Hz. In echo-planar imaging (EPI) as applied by all but one of the feedback studies, field inhomogeneities elicit distortions such as local shifts and compressions in the image. In contrast, spiral acquisition as applied by deCharms et al. [20] suffers from image blurring instead of shifts, because it uses a circular encoding scheme instead of the rectangular scheme used by EPI. The induced mis-registrations depend upon motion and, thus, can simulate BOLD signal changes by head motions [3]. Feedback might lead to learning of small movements or other manipulations of artefacts. Moreover, activations might be moved out of the ROI if local shifts are not corrected. Blurring in spiral imaging seems less problematic, because it does not shift the location but affects the extent only. Previously suggested distortion corrections were mainly based on a reference measurement assessing the magnetic field distribution (e.g., [42]). This static reference, however, cannot compensate for the dynamic aspect of the distortions which is of particular importance for an on-line BCI with feedback.

As a simple and fast technique which can be applied in real-time [92], we have presented a distortion correction using single-shot multi-echo EPI data [91]. Using alternating phase-encoding direction, images with opposite image distortions are obtained. By applying a fast and robust coregistration algorithm, dynamic correction for fluctua-

tions of the magnetic field can be calculated. No time-demanding reference scans—which only reflect the magnetic field inhomogeneities at one point in time—are required. In general, this development shows that more sophisticated and specifically tailored algorithms for real-time artefact suppression become available along with the demands of specialised applications.

In addition to distortions, inhomogeneities of the static magnetic field may cause signal dropouts, in particular if they are large. Signal dropouts cause deteriorated images and reduce BOLD sensitivity disproportionately [21]. Though it is possible to reduce these effects by adapted MR pulse sequences [21], speed or SNR are compromised. Posse et al. [69,71] employed a modified single-shot multi-echo EPI sequence with compensation gradients for the measurement and feedback of activity in the amygdala. Spiral-in/out acquisition techniques have been reported to reduce signal dropouts in fMRI but have not yet been applied for real-time applications [73]. As a simple solution, studies may restrict their ROIs to regions which do not exhibit strong susceptibility effects as in these areas signal intensity depends heavily on small movements. Otherwise, subjects might develop strategies to control these artefactual and localised signal changes instead of regulating their brain activity in feedback applications.

2.3.3. Respiration

Breathing influences the magnetic field strength in the head by the bulk motion of the thorax [32]. The respiration dependent shifts in the resonance frequency lead to global changes in signal intensity. Like the previously mentioned artefacts, certain respiratory patterns could influence the feedback signal. Subjects might use the effect of breathing to control signal time courses. Several strategies have been reported to reduce these effects in off-line data analysis (e.g., [7,32]). However, procedures that work on-line have not been published so far. The on-line distortion correction [91,92] accounting for dynamic off-resonance effects might reduce image artefacts caused by respiration, as well.

Moreover, changes in respiration like breath holding or hyperventilation may induce long-term changes in blood CO_2-concentration and, thus, affect neurovascular coupling and cerebral blood flow [43,70]. Yet, one study on neurofeedback measured blood CO_2-concentration levels and reported no significant changes [69]. Taken together, we consider respiration to be an important issue which is not completely resolved. As an initial approach, subjects should be instructed to breathe regularly and respiration should be monitored during the experiment.

3. Operant learning

In this chapter, we review the experimental designs of the fMRI neurofeedback experiments and relate them to general principles of operant conditioning [80].

"Operant conditioning typically involves the presentation of rewards (or punishments) *contingent* upon a specific behaviour of the organism. Conditioning is said to take place when the probability of an organism making a response has been modified by the contingency." ([79, p. 39])

The contingent reinforcement is necessary to change the rate of the rewarded response. An intrinsic reward may be the feedback of the physiologic variable (e.g., brain activity measured by EEG or fMRI) which can be further enhanced by generalised reinforcers such as monetary reward or social incentive. Studies on operant conditioning in animals, as well as biofeedback and EEG neurofeedback in human subjects indicate that the type of feedback and reward influence learning considerably.

First, minimal lags [60,76] and a high reliability [61] between the physiological response (brain activity) and the reward (feedback) facilitates learning (higher contingency). Second, increased cognitive load and processing due to a more complex information extraction from the feedback display might reduce learning. Third, the modality of the feedback influences learning. For instance in studies on self-regulation of SCPs, visual feedback improved learning over auditory feedback [39].

Fourth, certain schedules of reinforcement used for shaping and chaining might be applied to neurofeedback [20]. These reinforcement schedules can differentiate a complex physiological response by remodelling existing responses or constructing complex chains from simple responses. Shaping is a variant of operant conditioning widely used as a therapeutic tool for the treatment of various disorders, especially those affecting verbal behaviour. Instead of waiting for a subject to exhibit a desired behaviour, any response leading to the target or final behaviour is rewarded. In neurofeedback, shaping might be implemented by varying the task difficulty. For example, at the beginning even small increases of brain activity are rewarded, but as soon as minor increases have been successfully achieved higher levels of activity are required as a next step [20]. An operant chain is a sequence of learned responses and discriminative stimuli, with each learned response producing the discriminative stimulus for the successive response. Future studies might employ chaining of behaviour and break down a complex sequence of self-regulation tasks into different components which are learned and then integrated.

Fifth, in neurofeedback experiments, external factors such as selection of subjects (e.g., potential neuropsychological factors [18]), instructions prior and during the feedback sessions, interaction between subjects and experimenter, and, in general, the experimental environment have to be considered. Particularly in clinical applications, neurofeedback was embedded in a broader therapeutic approach, which takes into account important factors such as attitudes, motivation, and compliance [58].

3.1. Cognitive factors

The technical MRI environment in combination with loud imaging noise might impede learning and application of self-regulation. As a possible solution, subjects could be trained adaptively in a dummy scanner including artificial noise [40,41] or special MR imaging with decreased noise levels could be employed [11].

So far, only healthy volunteers and no patients participated in fMRI feedback studies—in some cases members of the research group were recruited [20,92,93]. Prior instructions were dependent on the type of feedback and trained brain activity. In case of continuous on-line feedback, subjects were informed about the technical and physiological delay between the neuronal activity and the feedback, e.g., delay between initiation of mental imagery and the feedback [20,92]. In case of the more complex feedback of functional maps, the subjects had to be instructed how to determine the extent of brain activity in the sensorimotor area, because they were naïve to neuroanatomy and fMRI [97]. When subjects should rely on covert processes, like motor imagery, to control brain activity, they were instructed to avoid overt movements [20,92]. Moreover, head motion and irregular respiratory patterns were discouraged in order to suppress artefacts [92].

Subjects were provided with initial strategies for control of brain activity which should guide behaviour; executed [97] or imagined [20,92] movements for motor areas (M1 and SMA), navigation and visual imagery for the PPA [92], and mood induction for the amygdala [69]. In one study, preparation included prior training of executed and imagined movements for 1 h [20]. In an exploratory study, we trained naïve subjects to control the differential feedback of SMA and PPA ([77], similar to [92]) without initial information about functional neuroanatomy or imagery strategies. Only out of four participants learned voluntary control without further information after few days of training, reporting the use of verbal recall of learning matters at school and non-verbal imagery of well-known rooms. For the other subjects, learning was accelerated by instructing them with visual and motor imagery strategies such as imagined fist clenching or navigation through outdoor scenes. Conceivably, effective imagery for the control of the target regions can speed up learning. In particular, feedback of local brain activity might disclose a specific relationship between control strategies and learned self-regulation.

Results of biofeedback studies are not conclusive whether and how initial strategies or verbal guidance influence and improve learning. In a study on heart rate control with biofeedback, subjects achieved larger heart rate changes when they were correctly informed about the target response, i.e., when they were aware that the feedback presented their heart rate [8]. However, Lacroix and Roberts [50] reported that instructions to use cognitive strategies were deleterious to control of both electrodermal and cardiac target responses. Physiological response patterns may vary considerably dependent on the provided strategy, as has been shown for the heart rate and EEG [79]. The influence of instructions might depend on the ability to label the effective control strategies verbally (for a discussion, see [49]). In self-regulation of SCPs, the conscious perception of the self-regulated brain activity seems to follow its control, i.e., patients could rate their performance correctly only after they had already acquired the self-regulation skill [45]. This suggests that verbal strategies are not necessary to regulate SCPs.

In general, brain activity—considered as a physiological response—should be accessible to operant conditioning regardless of verbalisation, because even in rats modification of neuronal firing rates was achieved [65]. In non-human primates, activity of single neurons [26] or ensembles of neurons (e.g., improvement of directional tuning [86]) was successfully modified by operant conditioning.

3.2. Feedback signal

3.2.1. Physiological target

Exploiting the high spatial resolution and whole-brain coverage of fMRI, feedback might be based on ROIs, complex patterns of brain activity or functional interactions between brain structures (see Section 4.1). So far, all studies aimed at neurofeedback of specific brain regions (for anatomical locations, see Fig. 1). This requires delineation of the target ROI. Magnetic resonance imaging allows for definition of the ROI by anatomical landmarks [69,93,97] or by the individual functional neuroanatomy based on a localiser experiment [20,92,95]. Simple motor tasks like finger tapping can be applied to localise motor areas [20,54,92]. For primary and higher visual areas, conditions can comprise distinct visual stimuli. For instance, the PPA was identified by contrasting the brain activity induced by visual presentation of houses with the activity due to presentation of faces [64,92]. Moreover, functional localisers allow for identification of some brain areas involved in higher cognitive or affective processing like the ACC [13,14] or medial superior frontal gyrus (mental calculation; [95]).

3.2.2. Delay of feedback

In the reviewed studies, lags between data acquisition and feedback varied from about one second [20,92,93] to one [69,97] or two minutes [95]. In general, an effective delay in the range of seconds cannot be avoided due to image acquisition and haemodynamic delay (see Section 2.1). Longer lags allow for temporal averaging of the fMRI data to increase SNR and, thus, the reliability of the feedback [69,97]. However, SNR might also be considerably increased by spatial averaging such as smoothing [69] or the choice of large target ROIs encompassing several voxels [20,92,93] such that short delays can be retained.

3.2.3. Modality of feedback

One study on fMRI neurofeedback employed verbal feedback by the experimenter [69], the other studies used visual feedback [20,92,93,95,97]. Due to the excessive background noise during imaging, detailed acoustic feedback might be restricted to pauses between scans. Reports from self-regulation of SCPs suggest that visual feedback supports learning better than acoustic feedback even in silent environments [39].

Parallel processing of visual feedback decreases cognitive processing times which might be further reduced by application of unambiguous and instantly recognizable stimuli. Feedback of functional maps of brain activity (for an exemplary map, see Fig. 3a) require prior training to interpret those and impose relatively high attentional demands to the entire visualisation [97]. Furthermore, only activations exceeding a preset threshold are shown which might mask small initial signal changes.

Simple analogue scrolling graphs and curves which depict the level of brain activity in a region increase the processing speed and immediate availability of information to the subject ([20,92,93], Fig. 3b). Alternatively, images, movies or games motivate the subject and increase the efficiency of the reward, e.g., a funny image of an Olympic weight lifter depicting the level of activity [20] or navigation through a 2D maze by generating specific patterns of BOLD activity [95]. Such rewards can be adapted to specific groups of subjects or patients. For instance, in a study at our laboratory, children suffering from epilepsy have been presented with a cartoon story during self-regulation of neuroelectric spiking activity [78]. Reduction of spike frequency was rewarded with continuation of the narrative; increase resulted in interruptions (indirect punishment).

Currently, we are investigating a novel type of feedback for fMRI signals which allows for scanning two subjects simultaneously while they compete in a video game (BOLD Brain Pong; [36]). Like in the well-known electronic game classic Pong, both subjects see the same screen depicting a tennis court, a moving ball, and two rackets. Instead of controlling the simplified tennis game with a joystick, subjects are instructed to move the racket to the correct position using different levels of BOLD activity. A previous study by Sorger et al. [82] supports the feasibility of this approach by demonstrating that humans are able to voluntarily modulate local brain activity at such specific target levels. Preliminary results indicate high hit rates (60–80%) during the Brain Pong game, reflecting accurate control of the BOLD signal. The high level of control suggests that playing a video game against another participant results in effective reinforcement and speeded learning. Indeed, subjects reported very high motivation.

3.3. Training and generalisation

Control of brain activity concerns both the spatial and the temporal domain. The training strategies have to consider both aspects.

3.3.1. Targets of self-regulation

Spatially resolved feedback can support control of focal brain activity and is provided as high resolution functional maps or display of mean activity in ROIs. If voluntary control of a single region or a combination of regions should be learned, feedback of mean activity within the ROI or a linear combination of the activity within different ROIs is suggested. In particular, control of a difference signal of two ROIs avoids global effects, because they cancel out [20,92]. Global signal changes might be caused by physiological artefacts such as different patterns of respiration [43]. Moreover, required unidirectional control, i.e., increase of activity in a single region [69,93,97] or increase of activity in a single region as compared to global activity [20], might be extended to bidirectional control of the feedback signal. For example, volunteers can be instructed to increase and decrease the activity in one region as compared to another region [55,92]. The bidirectional control is considered more specific, because general effects of the regulation task itself occur in both conditions, e.g., general effects of arousal and attention caused by task demands. Any of these effects cancel out comparing both tasks and only allow for either increasing or decreasing the signal but not for bidirectional regulation.

3.3.2. Timing of the self-regulation task

According to the choice of ROIs and their functional relevance, the self-regulation was related to motor [20,92,93], visual [92], cognitive [95] or emotional [69,93] processing and its modulation. The required duration of regulation and rest periods varied between 15 s [97] and 60 s [93]. This is not merely a technical aspect but relates to the time constant of the required physiological response and the time required for task switching. For instance, the short period in case of the overt motor task [97] and longer periods in the motor imagery task [20] or mood induction [69] reflect the type of cognitive and emotional task required—motor execution can be initiated and stopped quickly, self-induced sadness requires slow memory recall and emotional regulation [17,69]. Future studies might reduce the required regulation periods to single events, resembling event-related designs as often used in conventional fMRI [59].

3.3.3. Generalisation of the self-regulation skill

Experimental sessions on self-regulation in the absence of feedback can be used to assess the transfer of the learned control, i.e., to test whether regulation generalises to situations where no feedback is available. Kotchoubey et al. [44] have shown that patients with epilepsy trained to regulate SCPs for more than 30 sessions in the lab retain their self-control skill without any further training over 6 months. In similar experiments at our lab, the generalisation training during the last sessions included introduction of distracting radio noise, social conflict discussions of the experimenters during training, and imagery of seizure provoking situations. deCharms et al. [20] reported that

subjects were able to continue regulation of the BOLD signal in the absence of feedback. In a current study on regulation of the SMA and PPA [77], we find similar results pointing to a learned ability which remains stable without feedback. Preliminary results suggest that successful regulation is continued even when a distracting task is presented (see behavioural testing in Section 4.2). Indeed, generalisation and stability of the regulation skill is also evidenced by the ability to regulate the BOLD signal with high accuracy while competing in the BOLD Brain Pong video game [36] which demands additional processing such as planning of actions.

4. Findings and future directions

Real-time fMRI and fMRI-BCI neurofeedback is a rapidly evolving field. Thus, an outlook might be rather arbitrary and speculative. With respect to the current development, we suggest three main topics which need to be considered. First, many methodological issues still deserve improvement from image acquisition to feedback presentation. Unreliable feedback might mask the contingency from neuronal changes to the feedback signal. Second, with an improved technique, a higher specificity of the feedback signal to the targeted functional brain changes should facilitate control. This will allow for training of focal brain activity of arbitrary origin. Finally, well-controlled applications will show whether fMRI neurofeedback can add to the existing knowledge of cognitive neuroscience and be used to diagnose or treat disorders.

4.1. Developments in technique and design

As a new field of research, fMRI feedback involves both technical improvements and development of experimental designs.

With inexpensive availability of fast processors even sophisticated algorithms can be calculated in real-time. Thus, optimisation strategies will be available for feedback, e.g., estimation of the individual haemodynamic response [31] or independent component analysis [25]. Moreover, the real-time character can help to optimise imaging parameters interactively and specifically for ROIs [96]. In particular, techniques that render fMRI less sensitive to artefacts are of interest, e.g., biexponential mapping and prospective motion compensation [83,87]. Most of the technical improvements, however, go together with general advances in fMRI and are discussed elsewhere (for a review, see [38]).

4.1.1. Connectivity

The functional interaction of different areas might play a more important role than local activation during cognitive tasks and is impaired in neurofunctional and behavioural disorders (e.g., schizophrenia [27]). Thus, the neuroimaging community particularly emphasises imaging of connectivity parameters (e.g., dynamic causal modelling [28] and Granger causality [35]). Like any other parameter, a measure of coupling between two or more areas can be used as feedback parameter and possibly trained for modification. So far, this is limited by the again longer time constant and delay as correlation requires multiple data points. Moreover, the requirements on the SNR are higher as well. Nevertheless, periodic external stimuli can elicit network oscillations. Neurofeedback could be applied to modulate the dynamics of those oscillations. Such procedure would resemble more closely common EEG paradigms using frequency bands for feedback (e.g., [24]).

4.1.2. Specificity of self-regulation

Spatial specificity of fMRI is superior to that of EEG, because it can record from the entire brain volume with high spatial resolution [40,41]. Thus, effective learning should lead to a specific increase or decrease of activity in the ROI but not in other regions [20,93]. Differential feedback applies signal differences of ROIs and can be used to increase specificity, because global effects cancel out and are not rewarded [20,93].

Specificity of the behavioural effects should be evaluated across different behavioural tests in bidirectional self-regulation tasks, i.e., while subjects increase and decrease the (differential) activity. For instance, reaction times in a motor task should follow the voluntarily modulated activity in motor areas. Two behavioural tests may be applied in differential regulation of two areas. If each test was specifically designed for the respective area, double dissociation would be expected. In our example, the reaction times in a forced choice task could be recorded for the left and the right hand while regulating left versus right motor cortex—similar to a previous study on hemispheric control of SCP [76]. In this case, one might expect faster reactions of the hand contralateral to the hemisphere whose activity is increased. Below, we give an example of a single subject tested for reaction times and memory during self-regulation of SMA and PPA (Fig. 4).

4.1.3. Improving specificity

Specificity encompasses robustness against artefacts, sufficient regional resolution, and responsiveness to haemodynamic changes. Frequently, artefacts appear rather globally across the imaging volume, e.g., intensity fluctuations due to frequency shifts or movements are observed at different areas simultaneously. Previously, we suggested using differential measures between two areas [92]. Alternatively, real-time application of independent component analysis (ICA) may be used to filter out global effects [25]. Nevertheless, supervision of the data by the examiner is required to preclude artefacts as major source of self-regulated signal changes [69].

The presented systems using on-line feedback relied on static ROIs [20,92,93]. Indeed, the ROIs used were rectangles within a single slice. Learning, however, could be enhanced by using improved functional delineation of the

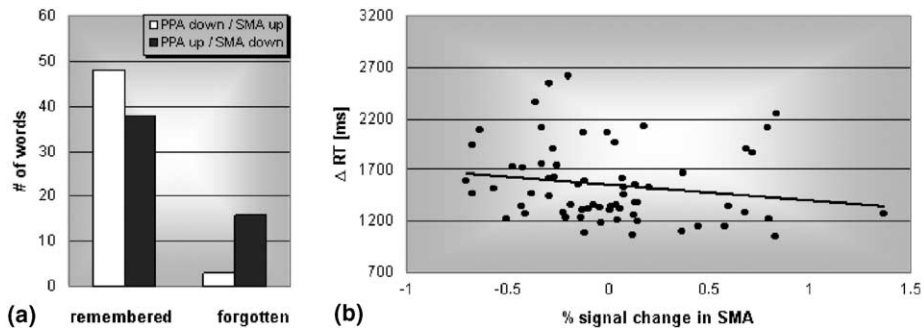

Fig. 4. Behavioural effects of self-regulation after 4 × 2 h training of differential control of supplementary motor area (SMA) and parahippocampal place area (PPA) in a single subject ([77], similar to [92]). (a) The down-regulation of PPA and up-regulation of SMA (PPA down/SMA up) condition led to significantly better incidental encoding of words. (b) The blood oxygen level-dependent (BOLD) signal at the SMA as independent variable predicted reaction times (RT) to acoustic events.

areas of interest or adaptive shaping strategies, i.e., reinforcement of behaviour step-wise approximating the target behaviour. For instance, after learning to control a rather large area, a sub-section of it might be regulated with less previous training. To allow for such a dynamic control of three-dimensional ROIs, coregistration to anatomical templates [30] or cortical surfaces [34] between sessions will be required.

According to the concept of shaping, the task demands or difficulty might be adjusted through training in order to direct behaviour and facilitate learning. For example, deCharms et al. [20] adapted the task difficulty to the subject's prior performance, i.e., a higher level of activation was required if the subject reached or exceeded the previous target level for three times. Subjects might also first learn to activate a specific brain region and later on learn to activate or deactivate another brain area at the same time.

4.1.4. Efficiency of fMRI feedback

To assess the specific contribution of neurofeedback to self-regulation, one can take different approaches: First, learning in an experimental group presented with feedback can be compared to learning in a control group provided with pseudo-feedback (also referred to as sham or false feedback). deCharms et al. [20] reported superior control of the sensorimotor region with contingent feedback as compared to pseudo-feedback. Blecker et al. [9] have recently studied the bidirectional control of Broca's area and reported an improved down-regulation in the experimental group as compared to the control group with pseudo-feedback. Yoo et al. [98] observed more extended BOLD signal changes in the auditory cortex when volunteers received contingent feedback instead of pseudo-feedback during attentional modulation to an auditory stimulus. An increase of voluntary control was reported for all studies except for the neurofeedback of self-induced sadness [69] which did not assess learning effects. Second, the feedback or reward may be varied throughout the experiment which should directly influence learning [61], e.g., modifying the monetary reward. Third, verbal reports of naïve subjects on the applied control strategies can be compared with the functional role of the regulated area, e.g., verbalised strategies for control of visual areas should relate to the visual modality.

Finally, feedback should be as specific as possible to avoid unwanted reactions such as motor or physical responses. For instance, during fMRI feedback, head motion should be minimised and still be corrected for in the analysis (see Section 2.3, [20,92,93]). Peripheral responses such as involuntary movements [20] or respiratory changes might be controlled by peripheral physiological recordings. To fully eliminate effects of motor and postural changes which may affect BOLD signals independent from the contingencies, completely paralysed patients may be studied or careful EMG control can be employed.

4.2. Future applications

Learning to regulate the BOLD response by itself is an important model as it can enhance our knowledge on mechanisms of operant learning and the physiology of neuroimaging. The control might be used to achieve behavioural effects and, thus, to discover direct links between regional brain architecture and its function. Clinically more relevant, voluntary control of such functions might be applied to improve brain functions in disorders. For instance, muscular feedback helped to reduce pain due to excessive tension [12]. In a similar vein, fMRI-BCI can be used to enhance brain functions required for emotional or cognitive processing or reduce excessive activity causing symptoms such as anxiety [75].

4.2.1. Behavioural effects

Studies using EEG for neurofeedback found that response latency during simple reaction time tasks were decreased locally for one hemisphere [76]. More importantly, improvements of socially significant behaviour were described. A recent study compared different types of EEG feedback and behavioural techniques in music students. They were randomly assigned to one technique, i.e., EEG

feedback training for theta over alpha, beta, or sensorimotor rhythm as opposed to physical, mental skills, or Alexander technique training. After 5 weeks practice in one of these techniques, the musical performance was rated in objective as well as in subjective—such as interpretive imagination—categories. Only the learned increase of theta over alpha bands was accompanied by improvements of all musical categories [24].

So far we have assessed emotional valence and arousal during regulation of ACC [93] in a methodological study on one subject (from the research group). For increased activity in the ACC, the rating of emotional state was more positive as compared to baseline conditions. However, the change in the affective state can be explained as a direct effect from the brain activation or a higher control attribution, i.e., a placebo effect. Moreover, a larger sample of naïve volunteers must be studied to allow for conclusive results.

A recent report by Maeda et al. [55] supports behavioural effects of ACC self-regulation. Using fMRI feedback, healthy subjects learned control over the level of activation in the rostral ACC, a region putatively involved in pain perception. When subjects voluntarily increased and decreased rostral ACC activation, they reported a corresponding change in pain perception elicited by an experimental noxious heat stimulus.

To overcome the subjective assessment of emotional states and verbal reports, we investigated incidental memory encoding during the control of a differential signal between SMA and PPA [77]. Based on functional neuroanatomy and imaging studies [90], the memory task should be sensitive to activity in the PPA. Word lists were presented to a subject who had learned fMRI-BCI control in four previous sessions (about 2 h each). She was merely instructed to detect pseudo-words while continuously up- or down-regulating the differential signal in alternating blocks. After this fMRI session for incidental encoding, the recognition of the presented words was studied. The memory test revealed that the down-regulation of PPA or up-regulation of SMA was accompanied by a significantly higher encoding rate (48 of 51 versus 38 of 54, $\chi^2 = 10.0$, $p < .01$; Fig. 4a). Whether the decline of memory function is due to interference at the level of the PPA, remains to be clarified.

4.2.2. Clinical applications

The example for a modification of memory functions by means of neurofeedback suggests the possibility for its use in memory disorders. Behavioural effects might be studied in any psychological or psychiatric disorder, in particular, if the neurobiological basis is known and causes abnormal levels of activity in specific brain regions. Indeed, after fMRI feedback training to modulate the rostral ACC activity, Maeda et al. [55] have reported a substantial decrease of symptoms in patients with chronic pain. Future studies have to show in which cases the level of activity can be normalised and if this leads to a reduction of symptoms. Depression is characterised by hypofunction in different areas, most consistently across studies at the genual part of the ACC (for a review, see [19]). Similarly, psychopathy is discussed to be related to hypoactivity of circumscribed brain regions [88].

Indeed, Phan et al. [67] showed that activation in the emotional system can be imaged in real-time. In the neurofeedback experiment on self-induced sadness [69], subjects' emotional self-ratings correlated with the activity in the amygdala. This is in line with the assumed role of the amygdala involved in negative emotions (e.g., [2]). Weiskopf et al. [93] reported changes in emotional valence and arousal during voluntary increase of activity at the ACC which might reflect its role in affective networks [13]. Training of the related structures might be applied to learn voluntary control of emotions. In addition to depression, emotional disturbances, anxiety and post-traumatic stress disorder (PTSD) might be addressed by fMRI feedback.

In the rehabilitation of brain lesions encompassing the motor system, the entire executive loop needs to recover as a whole. Despite the potential for recovery after stroke, relearning of lost arm function might not occur spontaneously. For instance, the constraint-induced movement therapy limits movements of the intact arm and, thus, promotes re-learning of motor functions [85]. Alternatively, successive reinforcement of parts of the target behaviour might be applied for a step-wise reactivation of the distinct brain circuits involved in arm movements [22]: Patients would learn to first reactivate pre-motor areas and in later steps the primary motor cortex, basal ganglia, and the cerebellum. Moreover, in a second step, shaping (reinforcement of the approximation to the target behaviour) might reduce mirror activation. These are additional BOLD activation patterns ipsilateral to the moved limb and seem not to contribute to performance [84]. Reorganisation could be modified by feedback to optimise performance and minimise side-effects, e.g., reorganisation coming along with phantom limb pain might be reversed [52,53]. In healthy volunteers neuroplasticity in the sensorimotor cortex was induced using fMRI feedback [20].

Yoo and Jolesz [97] reported modifications of the motor behaviour in response to fMRI feedback training. Hand movements were adjusted in order to expand activations in the sensorimotor cortex. The observed change in behaviour, i.e., recruiting more muscles and parts of the hand, might be applied for neurological rehabilitation. In the subject that learned control of SMA and PPA in four sessions as reported above [77], we also tested for effects on reaction times in an acoustically triggered bimanual motor task. An increase of activity at the SMA correlated with a speeded response ($\rho = -.32$, $N = 65$, $p < .01$; Fig. 4b). Taken together, differential feedback has specific behavioural effects in the motor and the cognitive domain. These effects might be beneficial in functional disorders of the brain.

5. Conclusion

Real-time fMRI allows for on-line feedback and voluntary control of brain signals. As a new experimental paradigm, local brain activation can be used as independent variable and functional consequences of the self-regulation on behaviour and cognition can be observed. A variety of data indicate that this technique can be used to modify behaviour. Technical progress including high-field fMRI, rapid data processing, and improved algorithms for data processing, data analysis, and feedback presentation renders the method widely available. So far feasibility has been shown; however, a benefit for cognitive neuroscience or clinical questions remains to be elaborated.

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