Manipulating motor performance and memory through real-time fMRI neurofeedback

Q1 Frank Scharnowski [a,b,*], Ralf Veit [c], Regine Zopf [d], Petra Studer [e], Simon Bock [c], Jörn Diedrichsen [f], Rainer Göbel [g,h], Klaus Mathiak [i], Niels Birbaumer [c,j], Nikolaus Weiskopf [k]

[a] Department of Radiology and Medical Informatics—CIBM, University of Geneva, Rue Gabrielle-Perret-G 4, CH-1211 Geneva 14, Switzerland
[b] Institute of Bioengineering, Swiss Institute of Technology (EPFL), STI-IBI Station 17, CH-1015 Lausanne, Switzerland
[c] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Gartenstrasse 29, 72074 Tübingen, Germany
[d] Department of Cognitive Science, Macquarie University, Sydney 2109, NSW, Australia
[e] Department of Child & Adolescent Mental Health, University Hospital of Erlangen, Schwabachanlage 6+10, 91054 Erlangen, Germany
[f] Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1 N 3AR, UK
[g] Department of Cognitive Neuroscience, Maastricht University, Maastricht 6200 MD, The Netherlands
[h] Maastricht Brain Imaging Center (M-BIC), Maastricht 6200 MD, The Netherlands
[i] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, RWTH Aachen University, Aachen, Germany
[j] Ospedale San Camillo, Istituto di Ricovero e Cura a Carattere Scientifico, Venezia-Lido, Italy
[k] Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, University College London, 12 Queen Square, London WC1 N 3BG, UK

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ABSTRACT

Task performance depends on ongoing brain activity which can be influenced by attention, arousal, or motivation. However, such modulating factors of cognitive efficiency are unspecific, can be difficult to control, and are not suitable to facilitate neural processing in a regionally specific manner. Here, we non-pharmacologically manipulated regionally specific brain activity using technically sophisticated real-time fMRI neurofeedback. This was accomplished by training participants to simultaneously control ongoing brain activity in circumscribed motor and memory-related brain areas, namely the supplementary motor area and the parahippocampal cortex. We found that learned voluntary control over these functionally distinct brain areas caused functionally specific behavioral effects, i.e. shortening of motor reaction times and specific interference with memory encoding. The neurofeedback approach goes beyond improving cognitive efficiency by unspecific psychological factors such as attention, arousal, or motivation. It allows for directly manipulating sustained activity of task-relevant brain regions in order to yield specific behavioral or cognitive effects.

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1. Introduction

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Perception, memory, and performing a motor task depend on specific patterns of brain activity. These patterns of brain activity can be divided into transient activity elicited by the stimuli or events, and sustained activity that precedes the stimuli/events. Recent evidence indicates that both pre- and post-stimulus activity contribute to task performance (Arieli, Sterkin, Grinvald, & Aertsen, 1996; Boly et al., 2007; Fox & Raichle, 2007; Fox, Snyder, Vincent, & Raichle, 2007; Hesselmann, Kell, Eger, & Kleinschmidt, 2008a; Hesselmann, Kell, & Kleinschmidt, 2008b; Ress, Backus, & Heeger, 2000). While the latter is largely determined by the stimulus characteristics itself, the former can be modulated by attention, arousal, and motivation (Broadbent, 1971; Freeman, 1933; James, 1890; Wundt, 1882). Although such modulating factors play an important role in task performance, they are rather general factors of cognitive efficiency that cannot facilitate regionally specific brain processes.

Here, we manipulated sustained brain activity in circumscribed brain regions by using real-time functional magnetic resonance imaging (fMRI) based neurofeedback. Rather than modulating sustained pre-stimulus activity in an unspecific way (e.g. via arousal),

* Corresponding author at: Swiss Institute of Technology Lausanne, Department of Bioengineering, EPFL/IBI-STI/GR-VDV, Station 17 Bât. BM.128, CH-1005 Lausanne, Switzerland . Tel.: +41787676749.
E-mail address: Frank.Scharnowski@epfl.ch (F. Scharnowski).

this new approach allowed us to train participants to voluntarily 'clamp' pre-stimulus levels of regionally specific brain activity at high or low levels. Until now, neurofeedback was mainly used to train self-regulation of autonomic functions or of specific electroencephalography (EEG) components, in order to communicate with severely paralyzed patients (Birbaumer et al., 1999; Birbaumer, Murguialday, & Cohen, 2008; Kübler, Kotchoubey, Kaiser, Wolpaw, & Birbaumer, 2001), to suppress epileptic activity (Kotchoubey et al., 2001; Sterman & Egner, 2006; Tan et al., 2009), or to treat symptoms of attention deficit hyperactivity disorder (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Gevensleben, Rothenberger, Moll, & Heinrich, 2012; Moriyama et al., 2012). However, neurofeedback with EEG is limited with respect to spatial specificity, and thus of the brain regions which can be targeted. Neurofeedback with real-time fMRI offers the advantage of learning to control spatially localized brain activity within the range of millimeters (Birbaumer, Ruiz, & Sitaram, 2013; deCharms, 2007, 2008; Sulzer et al., 2013a; Weiskopf et al., 2004; Weiskopf et al., 2007). So far, few studies have employed this technically challenging method, however, the existing ones have demonstrated the feasibility of self-regulating activation in specific brain areas. Some studies have additionally shown that self-regulation leads to behavioral effects that are specific to the functional role of the targeted cortical area (Bray, Shimojo, & O'Doherty, 2007; Caria et al., 2007; deCharms et al., 2005; Rota et al., 2009; Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012; Shibata, Watanabe, Sasaki, & Kawato, 2011; Weiskopf et al., 2003, 2004). Recently, studies have even demonstrated therapeutic effects of real-time fMRI neurofeedback training in chronic pain patients (deCharms et al., 2005), Parkinson's disease (Subramanian et al., 2011), tinnitus (Haller, Birbaumer, & Veit, 2010), and depression (Linden et al., 2012).

Most neurofeedback studies so far have trained participants to control activity within one region of interest (ROI). This was accomplished by either providing feedback from the ROI alone (Bray et al., 2007; Caria, Sitaram, Veit, Begliomini, & Birbaumer, 2010; Johnson et al., 2012; Johnston et al., 2011; Johnston, Boehm, Healy, Goebel, & Linden, 2010; Koush, Zvyagintsev, Dyck, Mathiak, & Mathiak, 2012; Mathiak et al., 2010; Subramanian et al., 2011; Weiskopf et al., 2003; Yoo et al., 2007; Yoo, Lee, O'Leary, Panych, & Jolesz, 2008), or by providing differential feedback between the ROI and either the contralateral homologue of the ROI (Chiew, LaConte, & Graham, 2012; Robineau et al., 2014) or some kind of background region (e.g. a reference slice) (Caria et al., 2007; deCharms et al., 2004; deCharms et al., 2005; Haller et al., 2010; Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011; Hampson et al., 2011; Rota et al., 2009; Veit et al., 2012). Differential feedback has the advantage that global effects such as breathing, heart rate, unspecific changes due to arousal, and head movements are less likely to cause artifactual self-regulation. This is because these sources of artifacts affect the ROI as well as the background region, and are canceled out with differential feedback. In the present study, we extended the use of differential feedback by now using a second, functionally unrelated ROI instead of an unspecific background region, and by also including bidirectional control of the feedback signal (participants learned to voluntarily up- and down-regulate the feedback signal). Such bidirectional control also excludes that self-regulation can arise from unspecific effects related to task demands, such as attention or arousal. Any unspecific effects that are related to task demands will only allow to either increase or decrease the differential feedback signal, but will not allow bidirectional control.

The ROIs we trained were the supplementary motor area (SMA), which is involved in the control of movement (Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008; Koeneke, Lutz, Wustenberg, & Jancke, 2004; Nachev, Kennard, & Husain, 2008; Tanji, 2001), and the parahippocampal cortex (PHC), which is involved in memory encoding of visual scenes (Brewer, Zhao, Desmond, Glover, &
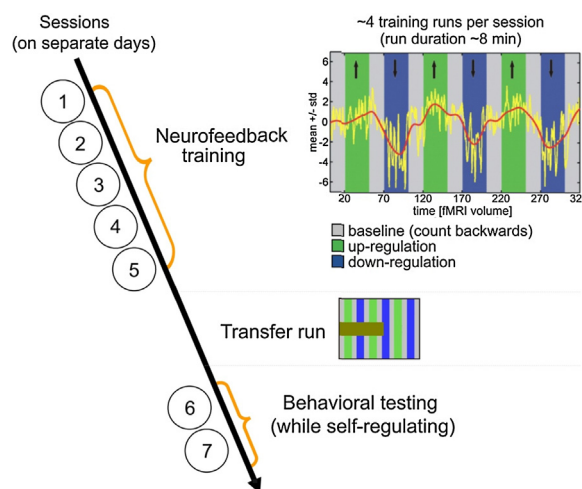
Fig. 1. *Experimental design.* In order to learn simultaneous control over the level of ongoing activity in the SMA and in the PHC, participants underwent 12–22 runs of neurofeedback training spread over the course of 4-6 days, until they reached a predefined threshold of successful self-regulation. Each scanning session lasted ~1 h. At the beginning of each neurofeedback training session, the ROIs were defined with functional localizers. Then, participants did on average 4 feedback runs of 8 min each per session. A feedback run was composed of 30 s baseline blocks (gray) interleaved with 45 s up- (green) and down-regulation (blue) blocks. The differential feedback signal was presented as a continuously updated yellow curve which was superimposed on the color-coded background illustrating the paradigm. For illustration purposes, a low-pass filtered (Gaussian FWHM =) version of the feedback signal is shown in red (this red curve and the black arrows were not presented during the experiment). After the training, participants tried self-regulation in the absence of feedback (transfer run), i.e. only the condition was indicated by a progress bar but not the feedback signal. Last, behavioral testing was performed in two separate scanning sessions on two separate days. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Gabrieli, 1998; Gabrieli, Brewer, Desmond, & Glover, 1997; Stern et al., 1996; Turk-Browne, Yi, & Chun, 2006) and words (Fernandez, Brewer, Zhao, Glover, & Gabrieli, 1999; Otten, Quayle, Akram, Ditewig, & Rugg, 2006; Wagner et al., 1998). Because these two ROIs serve different brain functions, our paradigm involves the simultaneous training of two functionally distinct brain areas. We hypothesize that simultaneous differential training of the SMA and the PHC will cause behavioral effects that are linked to the functional role of each trained ROI. Specifically, we hypothesized that higher levels of SMA activity cause faster motor reaction times, and that higher levels of PHC activity cause improved memory. To test this hypothesis, we examined whether exercising voluntary control over SMA and PHC after neurofeedback training caused specific performance changes in a motor reaction time task and in a word memory task, respectively (Fig. 1).

2. Materials and methods

2.1. Functional MRI data acquisition

All experiments were performed on a 3 T Magnetom Trio scanner, using a standard transmit-receive head coil (Siemens Healthcare, Erlangen, Germany). Functional data were acquired with a single-shot gradient echo planar imaging sequence (matrix size: 64×64; resolution: $3.3 \times 3.3 \times 5$ mm; 16 oblique transversal-coronal slices; slice thickness: 6 mm; slice gap: 1 mm; echo time TE: 35 ms; repetition time TR: 1500 ms; flip angle: 70°; receiver bandwidth: 2000 Hz/Px). For offline superposition of functional activations over anatomical details, we collected from each participant a high resolution T1-weighted structural scan of the whole brain (3D MDEFT; 1 mm isotropic resolution; matrix size: 256×240 mm; field of view: 256×240 mm; 176 sagittal partitions;