NeuroImage xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Dynamic reconfiguration of human brain functional networks through neurofeedback

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ARTICLE INFO

Article history:
Accepted 5 May 2013
Available online xxxx

Keywords:
Neurofeedback
Self-regulation
Functional connectivity
Real-time fMRI

ABSTRACT

Recent fMRI studies demonstrated that functional connectivity is altered following cognitive tasks (e.g., learning) or due to various neurological disorders. We tested whether real-time fMRI-based neurofeedback can be a tool to voluntarily reconfigure brain network interactions. To disentangle learning-related from regulation-related effects, we first trained participants to voluntarily regulate activity in the auditory cortex (training phase) and subsequently asked participants to exert learned voluntary self-regulation in the absence of feedback (transfer phase without learning).

Using independent component analysis (ICA), we found network reconfigurations (increases in functional network connectivity) during the neurofeedback training phase between the auditory target region and (1) the auditory pathway; (2) visual regions related to visual feedback processing; (3) insula related to introspection and self-regulation and (4) working memory and high-level visual attention areas related to cognitive effort. Interestingly, the auditory target region was identified as the hub of the reconfigured functional networks without a-priori assumptions. During the transfer phase, we again found specific functional connectivity reconfiguration between auditory and attention network confirming the specific effect of self-regulation on functional connectivity. Functional connectivity to working memory related networks was no longer altered consistent with the absent demand on working memory.

We demonstrate that neurofeedback learning is mediated by widespread changes in functional connectivity. In contrast, applying learned self-regulation involves more limited and specific network changes in an auditory setup intended as a model for tinnitus. Hence, neurofeedback training might be used to promote recovery from neurological disorders that are linked to abnormal patterns of brain connectivity.

Introduction

Studying how different brain areas interact may hold the key to understand how information is processed in the human brain. Recent developments in data analysis techniques have opened up exciting opportunities to investigate such functional connectivity with functional magnetic resonance imaging (fMRI). The techniques to study large-scale networks using fMRI can be divided into two main approaches. According to the first approach, functional connectivity is measured by interregional temporal correlations of the fMRI blood oxygenation level dependent (BOLD) signal (Biswal et al., 1995). This approach requires the choice of a seed region, for which correlation maps can be built. Among other findings, seed-region based approaches lead to the discovery of resting-state functional networks (Fox and Raichle, 2007). The second approach relies on multivariate and data-driven techniques such as independent component analysis (ICA) (Calhoun et al., 2001b; McKeown et al., 1998a, 1998b). ICA can be used to decompose the data into a set of spatial maps and associated time-courses without using pre-defined seed regions (Daubechies et al., 2009). Group-level ICA is a powerful technique to investigate distinct functional networks (Beckmann et al., 2005; Damoiseaux et al., 2006; Greicius et al., 2003).

Many fMRI studies exploring functional connectivity intrinsically assume a static organization. However, recent evidence suggests that functional connectivity can be modulated spontaneously (Raichle, 2010), by exogenous stimulation (Buchel et al., 1999), and by learning (Bassett et al., 2011; Lewis et al., 2009). Importantly, changes in functional connectivity have also been linked with the course of a variety of neurological diseases (Fox and Greicius, 2010) as well as the recovery from certain neurological diseases (Wang et al., 2010). Such

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1053-8119/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.neuroimage.2013.05.019

observations raise the possibility that learning-related changes in functional connectivity can help to accelerate the recovery. This is especially the case if the learning-related changes in functional connectivity can be targeted at the networks involved in the recovery.

A new and promising approach that allows targeting specific regions and networks directly is real-time fMRI (rt-fMRI) neurofeedback (deCharms, 2008; Weiskopf et al., 2004b). The basic principle of rt-fMRI neurofeedback is to present a biofeedback signal extracted online from fMRI BOLD measurements. With the help of such a signal, participants can learn self-regulation of BOLD activity by means of operant conditioning. Several studies have demonstrated the feasibility of self-regulating activity in specific brain areas using rt-fMRI neurofeedback (e.g., deCharms et al., 2004; Posse et al., 2003; Weiskopf et al., 2003, 2004a; Yoo and Jolesz, 2002). Some studies have even shown that self-regulation results in clinical benefits for specific neurological conditions such as chronic pain (deCharms et al., 2005), tinnitus (Haller et al., 2010), and Parkinson's disease (Subramanian et al., 2011). Further, there is preliminary evidence that learning self-regulation of brain activity can lead to changes in functional connectivity (Horovitz et al., 2010; Lee et al., 2011; Rota et al., 2011). However, the studies looking into changes in functional connectivity are limited for two reasons. Firstly, they applied seed-region approaches that limit the investigation of connectivity changes to pre-defined region of interests (ROIs). Secondly, they only investigated connectivity changes during the neurofeedback training phase but they did not look into such changes when participants applied learned self-regulation; i.e., when participants performed previously learned self-regulation without feedback. Especially with respect to clinical applications the transfer condition is more important than the training phase because learned self-regulation along with the accompanying changes in functional connectivity can be voluntarily applied by the patient.

Here we significantly extend the previous investigations of changes in functional connectivity due to neurofeedback by using data-driven techniques that do not require defining a seed region a priori. Because changes in functional connectivity during the neurofeedback training phase might be related to the neurofeedback per se, to learning mechanisms, or both, we included a transfer phase during which participants applied the previously learned strategy in the absence of feedback and hence absence of learning. We hypothesize that our data-driven approach—i.e., independent component analysis (ICA)—can identify changes in functional networks that are related to the neurofeedback target region, in particular, the auditory cortex. Further, we hypothesize that the functional connectivity changes during neurofeedback learning will differ from the changes during applied self-regulation; e.g., only the former will include changes in networks related to feedback processing and reinforcement learning while the latter will demonstrate changes in functional connectivity related to self-regulation.

Materials and methods

The setup and the experimental procedure were similar to a previously published study (Haller et al., 2010). For readability, the main points are repeated here. For further details, please see Haller et al. (2010). The data used in this study were collected for a previous experiment examining the impact of rt-fMRI on the default-mode network (Van De Ville et al., 2012).

Participants

Twelve healthy, right-handed individuals (mean age 28.4 years; range 24–33) with normal audition gave written informed consent to participate in the experiment, which was approved by the local ethics committee. Before the experiment, they received written instructions describing that they will learn to regulate their auditory cortex activity with the help of neurofeedback. The instructions included an explanation of the neurofeedback display and recommended as potential regulation strategies to direct attention away from the auditory perception. Further, we explained to the participants that the feedback was delayed by approximately 8 s (the hemodynamic delay plus the real-time analysis processing time).

fMRI data acquisition

All experiments were performed on a 3 T Magnetom Verio whole-body MR scanner, using a standard 12-channel receive head coil (Siemens Healthcare, Erlangen, Germany). Functional data were acquired with a single-shot gradient echo planar imaging sequence (matrix size: 64×64; isotropic resolution: $3 \times 3 \times 3$ mm; echo time TE: 40 ms, repetition time TR: 2000 ms with 130 repetitions for the auditory localizer runs, 195 repetitions for the training runs and 210 repetitions for the transfer runs). Additionally, we acquired an anatomical T1-weighted structural scan of the whole brain (MPRAGE; 1 mm isotropic resolution; matrix size 256×256; 176 sagittal partitions, TE: 3.4 ms, repetition time TR: 2000 ms, TI: 1000 ms).

The neurofeedback setup used Turbo BrainVoyager (Brain Innovations, Maastricht, The Netherlands) and custom scripts running on MATLAB (MathWorks Inc., Natick MA, USA). It allowed participants to observe BOLD signal changes in specific brain regions with a delay of less than 2 s from the acquisition of the image. Head motion was corrected in real-time using Turbo-BrainVoyager.

Experimental procedure

In the first scanning session, a standard fMRI auditory block-design paradigm was performed to identify each participant's primary auditory cortices. For this, we presented participants with 5 repetitions of 20 s bilateral auditory stimulation interleaved with 20 s resting baseline. The auditory stimulus was a sine tone of 1000 Hz and pulsating at 10 Hz, which is known to induce a strong and long-lasting BOLD response (Haller et al., 2006; Seifritz et al., 2002).

Next, participants took part in 4 rt-fMRI neurofeedback training runs per day repeated over 4 days (with approximately 1 week intervals between training sessions). The training runs were composed of a 30 s baseline block, followed by 4 repetitions of alternating blocks of 60 s down-regulation and 30 s baseline blocks. During the down-regulation blocks, the same pulsating sine tone of 1000 Hz as in the localizer runs was presented. Participants were presented feedback about their success, which indicated the percentage of signal change compared to the previous baseline block. The visual feedback display was continuously presented during the entire run.

After the neurofeedback training sessions, each participant performed a single self-regulation in the absence of feedback (transfer phase). While changes in connectivity during the training phase might conflate regulation and learning effects, the transfer runs allow assessing the effect of regulation without feedback and thus no further learning-related effects. In the transfer phase, we also included a counting-backwards condition; i.e., the participants were asked to mentally count backwards from 100 in steps of −7. The purpose of this task was to ascertain a control task with cognitive and working memory load, without the specific application of the previously learned self-regulation strategy. The transfer runs were composed of five 20 s down-regulation (D) blocks interleaved with five counting (C) backwards blocks and eleven rest (R) blocks of the same duration in a RDRCR… design. The block length during the transfer runs was 20 s as compared to 60 s during the training runs. During the training runs, participants were asked to try out different down-regulation strategies in the presence of neurofeedback. Therefore, we opted for regulation epochs of 60 s. In contrast, as we expect participants to regulate faster during the transfer runs without feedback and further ability to learn, we opted for shorter regulation epochs of 20 s in agreement with standard block-design fMRI studies (Amaro and Barker, 2006).

Please cite this article as: Haller, S., et al., Dynamic reconfiguration of human brain functional networks through neurofeedback, NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.05.019