Increasing cortical activity in auditory areas through neurofeedback functional magnetic resonance imaging

Seung-Schik Yoo\(^a\), Heather M. O’Leary\(^a\), Ty Fairneny\(^b\), Nan-Kuei Chen\(^a\), Lawrence P. Panynch\(^a\), HyunWook Park\(^d\) and Ferenc A. Jolesz\(^a\)

\(^a\)Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, \(^b\)Department of Biomedical Engineering, Boston University, Boston, Massachusetts, USA, Departments of \(^c\)BioSystems and \(^d\)Electrical Engineering and Computer Science, Korea Advanced Institute of Science and Technology, Daejeon, Korea

Correspondence and requests for reprints to Dr Seung-Schik Yoo, PhD, MBA, Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St Boston, MA 02115, USA
Tel: +617 525 3308; fax: +617 525 3330; e-mail: yoo@bwh.harvard.edu

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We report a functional magnetic resonance imaging method to deliver task-specific brain activities as biofeedback signals to guide individuals to increase cortical activity in auditory areas during sound stimulation. A total of 11 study participants underwent multiple functional magnetic resonance imaging scan sessions, while the changes in the activated cortical volume within the primary and secondary auditory areas were fed back to them between scan sessions. On the basis of the feedback information, participants attempted to increase the number of significant voxels during the subsequent trial sessions by adjusting their level of attention to the auditory stimuli. Results showed that the group of individuals who received the feedback were able to increase the activation volume and blood oxygenation level-dependent signal to a greater degree than the control group.

Keywords: attention, biofeedback, brain–computer interface, brain mapping, learning and memory

Introduction

Neurofeedback, the feedback of biological signals associated with one’s own brain function, has the potential to help individuals learn specific mental strategies to self-regulate their brain function. Although its clinical utility is still an active area of investigation, neurofeedback has already been applied to the management of attention deficit and hyperactivity disorder [1] and the treatment of phobic anxiety or seizure-related disorders [2,3]. With the advent of functional neuroimaging techniques, regional brain activities can be characterized in vivo and made available as a feedback signal source.

Capitalizing upon noninvasive means to provide a high-resolution definition of cortical function, combined with a real-time data processing capability [4], functional magnetic resonance imaging (fMRI) has been successfully deployed for several neurofeedback experiments. These experiments include the regulation of activity in somatomotor areas during hand motor tasks [5] and in rostral–ventral and dorsal parts of the anterior cingulate cortex associated with the regulation of affective states [4] and pain [6]. Posse et al. [7] studied an active process of induced emotion by measuring the magnetic resonance signal changes associated with self-regulation. deCharms and colleagues [8] have shown that the performance strategy can be learned and retained (even after the trial sessions) to enhance activation in the somatomotor cortex during hand imagery tasks.

In this study, we were motivated to test the feasibility of using neurofeedback fMRI for the regulation of cortical activation associated with attention, especially with respect to auditory attention. Active listening, which involves selective attention to specific spectro-temporal changes during the stream of sound stimulation, has been reported to increase in magnitude and volume of activation in corresponding auditory areas, compared with passive, unattended listening [9,10]. Auditory attention in the absence of any external cues or interference, however, may be difficult to perform, along with the possibility of habituation-related signal reduction [11]. We postulated that fMRI neurofeedback would enable individuals to increase the number of activated voxels associated with
auditory attention when compared with a demographically matched control group who were not exposed to the neurofeedback.

**Method**

**Overview and recruitment of study participants**

The study was conducted in accordance with the ethical standards set forth by the Institutional Review Board of Partners Healthcare. A total of 22 healthy volunteers (eight females; mean age 23.4 ± 5.2 years) without a history of neurological/hearing disorders participated in the study. The participants were randomly assigned and divided into two groups – one undergoing neurofeedback and the other undergoing the same task without neurofeedback. Participants’ demographic features were matched in terms of sex, age, and handedness. As neurofeedback involved an element of attention and cognitive learning, we also matched the participants in terms of level of education and scores obtained from a Digit Span and Letter–Number Sequencing Test using the Wechsler Adult Intelligence Scale (WAIS-R: The Psychological Co., San Antonio, Texas, USA).

**Magnetic resonance imaging and processing**

Experiments were conducted using a 3-T magnetic resonance system (GE Medical, Waukesha, Wisconsin, USA). All fMRI data were acquired using a gradient-echo echo planar imaging sequence (TR/TE=1500/40 ms, flip angle=80°, 22 × 22 cm field-of-view, 64 × 64 matrix) to detect the blood oxygenation level-dependent (BOLD) signal changes associated with neural activation. Twenty axial slices with 5 mm thickness (1 mm gap) were acquired to image the whole brain volume. A total of 74 volume images were acquired (scan time 1 min 52 s), and the first four volumetric data were excluded from further data processing to allow for T1 signal equilibration. T1-weighted spin echo images (TR/TE=500 ms/minimum, 256 × 128 matrix, 6 mm thick) covering the same brain volume were acquired to assist in the identification of regions of interest (ROIs) and the normalization of functional data. The echo planar imaging data were reconstructed and processed immediately after each scan session (within 10 s) using the method reported previously [5,12]. Real-time data processing and update upon each TR period could also be deployed to provide neurofeedback signals, but it may suffer from confounding effects of transient neural activity or noise [13]. Given the exploratory nature of the study, we used the activation results obtained from a complete scan session to constitute neurofeedback information.

**Experimental design and stimulation paradigm**

Participating individuals underwent multiple scan sessions, which consisted of three baseline sessions, five activation-regulation trial sessions, and three post-trial baseline fMRI sessions (as shown in Fig. 1). In each scan session, participants were given identical auditory stimulation, which consisted of four blocks of amplitude-modulated auditory stimuli (900 Hz tone, modulated at 6 Hz with a range of 47.5 dB ± 30% sound pressure level), interleaved with three blocks of both frequency-modulated (modulated at 6 Hz with a range of 900 Hz ± 12%) and amplitude-modulated (modulated at 6 Hz with a range of 72.5 dB sound pressure level ± 30%) auditory stimuli were presented binaurally via headsets (Avotec Inc., Stuart, Florida, USA). The use of the modulated sounds instead of static tones or silence was intended to help participants engage to the task without distraction.

Recruited participants in both testing groups were familiarized with the timing and the nature of stimulation using an identical set of instructions. Then, a reference fMRI scan was conducted while the participant passively listened to the incoming auditory stimulation. At the end of the reference session, a t-test was applied to the temporal data sets across the whole image volume, and statistical significance of the level of activation was determined at $P<10^{-3}$. On the basis of both anatomical MRI and functional maps, the target auditory areas were manually segmented to include the left primary and secondary auditory areas in the transverse superior temporal gyrus, as well as the planum temporale and planum polare. The ROI was selected from the left hemisphere on the basis of the documented leftward dominance associated with auditory processing for right-handed individuals [14]. The same stimulation paradigm, imaging parameters, and statistical threshold condition ($P<10^{-3}$, no volume corrections) were used throughout all sessions.

After ROI definition, three pre-trial sessions were conducted to measure the baseline activation level. During these sessions, participants were asked to passively listen to the incoming auditory stimulation as they did during the reference scan. After establishing the baseline activation for passive listening, participants underwent five regulation trial sessions (labeled 4–8 in Fig. 1) in which the participants were instructed to pay attention to only blocks containing both frequency-modulated and amplitude-modulated sounds.

For the neurofeedback group, the changes in detected activation volume from each of the trial sessions were converted to a percentage value with respect to the averaged activation volume acquired from three pre-trial

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**Fig. 1** An outline of the experimental design. The upper panel illustrates the block-based design paradigm used in each scan session. The lower panel illustrates the flow of the experiment. The arrowheads indicate the times at which the feedback information was delivered (for the neurofeedback group only). ROI, region of interest.
sessions. These percentage values were then fed back to the participants via the computer-generated voice at the end of each trial session: ‘You have performed at ____ percent increase from the baseline session’. This allowed the participants to evaluate the effectiveness of their regulatory efforts at the completion of each trial session. The minimum target regulatory level was instructed to be at a 40% increase from the baseline sessions (for example, more than 140 activated voxels if 100 voxels were activated during the pre-trial sessions) considering the upper limit of normal variation in activation volume observed from previous studies [15,16]. Guided by the feedback information, the participants engaged in the attention tasks to increase the volume of activation within the ROI. For the control group (who were blind to the existence of the neurofeedback method), the participants were instructed to pay attention, with their best effort, to the blocks containing both frequency-modulated and amplitude-modulated sounds without feedback information. Otherwise, the same scan protocols were administered. Upon completion of the attention trials, three post-trial fMRI sessions using passive listening were given to all participants to examine the recovery of baseline activity.

At the end of the study, all participants were briefly interviewed about the task strategy that they believed to be the most effective for achieving the goal. In spite of the use of the near real-time fMRI, the total scan time (including all the instructions) took approximately 40 min. An attempt to add other types of regulation trials, such as a participant’s attempt to decrease the number of activated voxels, would have significantly increased the scan time. Therefore, given the exploratory nature of this experiment, only one type of regulation was tested.

Offline functional magnetic resonance imaging data processing
Using SPM99, we processed the data offline to examine the neural substrates involved in the neurofeedback task. First, we chose three sets of the fMRI session data – a set from each of the pre-trial and post-trial sessions at the median level of activation (in terms of activation volume), and the last (fifth) trial session data representing the regulation trials. Each set of axial images for each participant was realigned to the first image, co-registered with the corresponding T1-weighted images, spatially normalized to MNI (Montreal Neurological Institute) space [17], and spatially smoothed (7-mm isotropic Gaussian kernel). Individual contrast images were first produced by comparing the task-dependent activation for each participant separately. These contrast images were then entered into a second-level group analysis using a random-effects model [18], comparing (a) pre-trial and post-trial sessions within each group, (b) pre-trial sessions between two participant groups, and (c) attention trial session and the pre-trial session. The last contrast was designed to elucidate the neural substrates selectively activated by the neurofeedback. To control for type I error through multiple comparisons, regions of significant difference were identified using a corrected, joint expected probability distribution of extent (P < 0.05) and height (P < 0.005; Z score > 2.58).

Results
Evaluation of online data
Individual task results, shown in terms of the percentage increase in activation volume, are depicted in Fig. 2. During the attention trials, several participants (n=7) in the control group actually attained the designated level of regulation, but the occurrence of these incidents was rather random among attention trials. Only three participants in the control group (participant nos. 2, 4, and 9) were able to sustain an increased volume of activation to the end of trial sessions. A few participants in the control group (for example, participant nos. 1, 3, 5, and 7) even showed a reduction in the activated volume during the attention trial. On the other hand, most of the participants under the neurofeedback procedure (except participant no. 7) were able to achieve or exceed the required target level of regulation.

Task strategy and attention regulation
On the basis of a survey, participants under neurofeedback expressed that the feedback was useful to change or maintain the task strategies. Reported initial task strategies were counting the number of pitches or a mental generation of similar sounds along with the presented sound. The participants, however, later adopted strategies that are cognitively more convergent: attending to the pitch/tone of the sound component itself (n=4), hearing sound as though the sound level is played in ‘low volume’ (n=3), or hearing ‘from a distance’ (n=2). Interestingly, all these strategies resembled the state of selective attention in the midst of interfering conditions or cues. On the other hand,
the task strategies reported by all 11 participants in the control group varied extensively and inconsistently.

**Offline data processing**

In order to examine the group-averaged trend in regulation trials, the activation volume and the BOLD contrast was measured from the ROI, and averaged across the individuals (in Fig. 3). No difference was observed in these measures between baseline and post-trial sessions (each sampled at median value among three sessions) according to paired t-tests (all \( P > 0.05; t < 0.72 \)). Repeated-measures analysis of variance (Matlab, Natick, Massachusetts, USA) was performed within each group, comparing the results obtained from the representative pre-trial baseline session with respect to the trial sessions 1–5. The analysis showed that a significant increase was observed at the last (fifth) trial session in case of volume of activation (\( P < 0.02; F > 2.93 \)), and from the fourth trial session in terms of the BOLD signal (\( P < 0.03; F > 2.82 \)) from the neurofeedback group. Participants in the control group could not achieve the desired level of regulation during the attention trials.

The detailed neural substrates activated during baseline and sampled trial conditions from each group are listed in Table 1. SPM random effect analysis comparing baseline and post-trial sessions showed no difference in activation from the sessions, therefore confirming that consistent baseline activation was established for both groups (\( Z < 2.58 \)).

Between-group analyses (paired t-test) on the sampled baseline condition data also suggested that there was no group difference in activation during the baseline sessions.

**Discussion**

We have demonstrated that neurofeedback (as measured by the activation volume in the primary and secondary auditory areas) effectively helped individuals to attain the desired level of increase in cortical activity within the target areas. The control group of participants, in the absence of any guideline, used rather random strategies, and their manifestation in cortical activation varied accordingly (in Fig. 2). As for the number of trial sessions needed to reach the desired level of regulation, participants were able to learn to change their cognitive strategies after three or four sessions of neurofeedback trials (in Fig. 3). We anticipate that the number of trials necessary to achieve the designated regulatory level would vary according to individuals and types of tasks.

Offline data analysis revealed that the attention trials performed by the neurofeedback group increased the activation volume in the left auditory areas and other extratemporal areas. Among the detected neural substrates, the planum polare and temporale have been implicated in the dichotic listening tasks with selective auditory attention [19]. This suggests that participants may have engaged similar strategies used for selective attention to target cues.

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**Fig. 3** The measured activation volume (thresholded at \( P < 0.0001 \)) from the region of interest (ROI), averaged across participants for 11 scan sessions (x-axis) for (a) the neurofeedback group and (b) the control group (standard deviation as shown in the bar). The measured blood oxygenation level-dependent (BOLD) signal contrast, averaged across participants for 11 scan sessions, was plotted for (c) the neurofeedback group and for (d) the control group. Thick solid bars indicate the attention modulation trials (sessions 4–8). Asterisks (*) indicate the statistically significant (\( P < 0.03; F > 2.82 \) repeated-measures analysis of variance) increase from the baseline conditions.
Scores were converted to relevant Talairach coordinates and regulation conditions for both the neurofeedback and control groups.

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>Neurofeedback group baseline</th>
<th>Z score</th>
<th>Control group baseline</th>
<th>Z score</th>
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<tbody>
<tr>
<td>Primary auditory cortex</td>
<td>55  -17  11  4</td>
<td>3.23</td>
<td>53  -20  3</td>
<td>3.63</td>
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<tr>
<td>Planum temporale</td>
<td>50  -31  17  7</td>
<td>4.55</td>
<td>53  -31  9</td>
<td>3.89</td>
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<tr>
<td></td>
<td>-38  -29  7</td>
<td>4.14</td>
<td>-42  -33  9</td>
<td>4.15</td>
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</table>

<table>
<thead>
<tr>
<th>Anatomy</th>
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<th>Z score</th>
<th>Control group trial</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary auditory cortex</td>
<td>46  -21  5</td>
<td>4.43</td>
<td>55  -16  3</td>
<td>4.14</td>
</tr>
<tr>
<td>Planum temporale</td>
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<td>3.84</td>
<td>55  -20  3</td>
<td>3.47</td>
</tr>
<tr>
<td>Planum polare</td>
<td>-44  -36  11</td>
<td>4.28</td>
<td>-44  -34  10</td>
<td>4.22</td>
</tr>
<tr>
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<td>-62  -4  0</td>
<td>3.49</td>
<td></td>
<td></td>
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<tr>
<td>Superior frontal gyrus</td>
<td>-23  9</td>
<td>3.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BA46)</td>
<td>1  8  49</td>
<td>3.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>-36  47  25</td>
<td>3.67</td>
<td></td>
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<tr>
<td>(BA10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate gyrus (BA32)</td>
<td>2  21  38</td>
<td>3.21</td>
<td></td>
<td></td>
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<tr>
<td>Cerebellum</td>
<td>-24  -65  25</td>
<td>3.32</td>
<td></td>
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</table>

*p Scores were converted to relevant Z scores (Z), at a threshold of *P < 0.005 (Z > 2.58) with *P < 0.05 extent correction. BA, Brodmann’s area.

In the midst of interfering/competing stimuli. The activation of the caudate–putamen complex during the attention trials also supports the findings from a recent investigation, which showed the implication of functional or structural abnormalities of the basal ganglia in attention deficits [20]. We believe that these extra-temporal neural circuitries, in combination with the auditory areas, could later serve as regulatory markers for attention regulation using similar neurofeedback approaches.

In this study, the volume of the activated area was used as the measure for successful regulation instead of the magnitude of the BOLD signal contrast. Our retrospective analysis of the BOLD signal contrasts (Fig. 3c and d), however, shows that the BOLD signal could be used to measure the regulation of cortical activation. The use of real-time display of the BOLD signal itself will greatly expedite the procedure, allowing for more regulatory options (such as a decrease in cortical activity) for a given scan time.

We also identified several other issues that still need to be addressed in future studies: for example, (a) the presence of the scanner background noise that may confound the effect of attention [21], (b) the choice of auditory stimulation that could lead to hemispheric differences in activation according to differential temporal and spectral specificity [22], and (c) the significance of using sham neurofeedback (such as deliberate feedback of false/irrelevant signals [6,8]) as alternative control conditions to examine the presence of any placebo effects. A data acquisition scheme such as ‘sparse sampling’ [23] will be helpful to dissociate the ambient scanner noise from the main effect of auditory attention. In addition, the use of different types of auditory stimulation with real-time monitoring of multiple regulatory areas will help to elucidate the general effect of neurofeedback on auditory attention.

**Conclusion**

This study introduces the possibility of neurofeedback-guided cortical functional regulation, especially in the realm of sensory attention. The concept of neuroimaging-based neurofeedback, by exploring novel task paradigms, can be applied to study various aspects of human cognition, emotion, and behavior. Planning rehabilitation strategies and monitoring the functional recovery/reorganization after a central nervous system injury is also an important future application of the fMRI neurofeedback approach.

**References**


