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Continuous vs. intermittent neurofeedback to regulate auditory cortex activity of tinnitus patients using real-time fMRI - A pilot study

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ABSTRACT

The emerging technique of real-time fMRI neurofeedback trains individuals to regulate their own brain activity via feedback from an fMRI measure of neural activity. Optimum feedback presentation has yet to be determined, particularly when working with clinical populations. To this end, we compared continuous against intermittent feedback in subjects with tinnitus.

Fourteen participants with tinnitus completed the whole experiment consisting of nine runs (3 runs × 3 days). Prior to the neurofeedback, the target region was localized within the auditory cortex using auditory stimulation (1 kHz tone pulsating at 6 Hz) in an ON-OFF block design. During neurofeedback runs, participants received either continuous ($n = 7$, age 46.84 ± 12.01, Tinnitus Functional Index (TFI) 49.43 ± 15.70) or intermittent feedback (only after the regulation block) ($n = 7$, age 47.42 ± 12.39, TFI 49.82 ± 20.28). Participants were asked to decrease auditory cortex activity that was presented to them by a moving bar. In the first and the last session, participants also underwent arterial spin labeling (ASL) and resting-state fMRI imaging. We assessed tinnitus severity using the TFI questionnaire before all sessions, directly after all sessions and six weeks after all sessions. We then compared neuroimaging results from neurofeedback using a general linear model (GLM) and region-of-interest analysis as well as behavior measures employing a repeated-measures ANOVA. In addition, we looked at the seed-based connectivity of the auditory cortex using resting-state data and the cerebral blood flow using ASL data.

GLM group analysis revealed that a considerable part of the target region within the auditory cortex was significantly deactivated during neurofeedback. When comparing continuous and intermittent feedback groups, the continuous group showed a stronger deactivation of parts of the target region, specifically the secondary auditory cortex. This result was confirmed in the region-of-interest analysis that showed a significant down-regulation effect for the continuous but not the intermittent group. Additionally, continuous feedback led to a slightly stronger effect over time while intermittent feedback showed best results in the first session. Behaviorally, there was no significant effect on the total TFI score, though on a descriptive level TFI scores tended to decrease after all sessions and in the six weeks follow up in the continuous group. Seed-based connectivity with a fixed-effects analysis revealed that functional connectivity increased over sessions in the posterior cingulate cortex, premotor area and part of the insula when looking at all patients while cerebral blood flow did not change significantly over time.

Overall, these results show that continuous feedback is suitable for long-term neurofeedback experiments while intermittent feedback presentation promises good results for single session experiments when using the auditory cortex as a target region. In particular, the down-regulation effect is more pronounced in the secondary auditory cortex, which might be more susceptible to voluntary modulation in comparison to a primary sensory region.

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1. Introduction

Real-time fMRI neurofeedback allows for voluntary control over a targeted brain region (Sulzer et al., 2013; Sitaram et al., 2016). This technique could one day be employed as a supplementary treatment for a range of disorders with known brain activity alterations and currently limited treatment options. Promising results have already been shown for several disorders including depression, obsessive-compulsive disorder and stroke rehabilitation (Linden et al., 2012, Sitaram et al., 2012, Buyukturkoglu et al., 2015).

As clinical real-time fMRI is still in its early days, there are still a lot of open questions concerning the optimal methodology. One issue concerns the feedback presentation timing of real-time fMRI neurofeedback. The vast majority of studies use continuous feedback that is updated with each new volume that is acquired. However, one study in healthy participants reported that intermittent feedback, defined as the mean feedback of the self-regulation period presented after regulation, was superior to continuous feedback when using the left premotor cortex as a target region and using a single session of feedback (Johnson et al., 2012). Other studies later confirmed that intermittent feedback can be used to elicit significant self-regulation effects (Koush et al., 2013, Koush et al., 2015).

There are a few arguments that would support this idea. When subjects do not have to pay attention to the feedback (which has an intrinsic time lag of around 6 s due to the hemodynamic delay in fMRI) during regulation, they might be able to concentrate more deeply on the task of self-regulation. In addition, reward processing as induced by feedback presentation will not confound brain activity during the regulation period in this setup. However, there are also factors in favor of continuous feedback. It provides a more direct feedback allowing the subjects to connect certain short-time actions or thoughts to be linked to an improvement in feedback, while intermittent feedback only gives an average feedback over the whole regulation block. Therefore, especially implicit learning might be much easier with continuous feedback as rapidly changing internal states and feedback can be compared internally over the whole regulation period rather than just getting one value as a feedback for the internal stages over the whole period. Moreover, the continuous feedback allows participants to change their strategy within one block if they observe that the current strategy is not effective. Thereby, they can optimize their strategy faster. If participants change their strategy within one block when provided with intermittent feedback, it is unclear to the participant which of the used strategies drive the feedback value most. Therefore, for intermittent feedback it is necessary to instruct participants to keep to one strategy throughout the block.

Intermittent and continuous real-time fMRI feedback presentation has never been directly compared in a clinical population. As healthy subject studies often suffer from a bias towards young and healthy participants, they are not very suitable to make assumptions about the general population and, notably, patients (Henrich et al., 2010). In addition, it is currently unclear whether the results obtained by Johnson et al. will also hold true for other target regions and when more than one neurofeedback session is conducted. Here, we therefore compare continuous and intermittent feedback in a clinical population, namely in 2 groups of 7 tinnitus patients in a total of 9 runs over 3 training days.

Tinnitus is a disease where patients perceive a sound even though there is no physical source for this sound. It may substantially reduce the quality of life, particularly when complicated with co-morbidities such as sleep disturbance, anxiety or depression (Langguth, 2011). Tinnitus may occur after a variety of cochlear pathologies, such as acoustic trauma and infection, among others, but can also occur without any apparent cause. The current hypothesis is that due to damage to the cochlea (even small damage that does not result in a significant hearing loss) the input to the auditory brain network is reduced (Henry et al., 2014). In an attempt to keep the input-output homeostasis the auditory input is amplified to an amount that the spontaneous firing rate at rest is enough to elicit the percept of a sound in the auditory network (Schaette and Kempter, 2006, Yang et al., 2011). In agreement with this hypothesis, it has been shown in animal studies and in humans that the auditory network, including the auditory cortex, is hyperactive in tinnitus (Gu et al., 2010, Eggermont, 2015). Transcranial magnetic stimulation (TMS) of the hyper-activated auditory cortex may reduce tinnitus symptoms (Plewnia et al., 2003, Londero et al., 2006, Forogh et al., 2014, Yilmaz et al., 2014). As rtfMRI could also be used as a way to reduce this hyperactivity, auditory cortex down-regulation via neurofeedback may be a suitable supplementary therapy for tinnitus.

A previous pilot study with a single fMRI neurofeedback session showed that it is possible to down-regulate the auditory cortex for five out of six tinnitus patients (Haller et al., 2010). In a two of these subjects the down-regulation was even accompanied by a decrease in tinnitus symptoms. Given this initial success, tinnitus seems a good model disease for clinical applications of neurofeedback, as the disease is rather common, does not induce strong physical impairments in patients (as e.g. in stroke patients) and the target region is easy to localize. We therefore recruited tinnitus patients for a neurofeedback experiment and compared between intermittent and continuous feedback in a clinical setting with several neurofeedback sessions.

2. Material and methods

2.1. Participants

The local ethics committee in Geneva approved this study. Fourteen subjects (mean age: 47.17 ± 11.73, 3 female) were randomly assigned to one of two groups receiving either intermittent or continuous feedback. All subjects gave written informed consent. The main demographic features of both groups are compared in Table 1.

Subjects had no to moderate hearing loss and there was no significant difference in hearing loss between the two groups (for Audiogram see Supplementary Fig. 1). Exclusion criteria included pregnancy, severe neurological or internal disorders and contraindications for MR-measurements. All participants received financial compensation for the study. Baseline fMRI activity was compared between groups to exclude pre-existing differences and no significant differences were detected.

2.2. Real-time experiment

In order to identify the auditory cortex, a functional localizer run was performed prior to neurofeedback runs. Subjects heard a 1 kHz tone pulsating at 6 Hz in an ON-OFF Block design with 6 blocks of 20 second stimulation followed by 20 s of rest each. A GLM was computed for the functional localizer using SPM8 (UCL, London, UK) to identify the bilateral auditory cortex. The contrast was thresholded at $p < 0.05$ FWE-corrected to obtain the region-of-interest used for the following real-time experiment. In some cases (8 out of a total of 42 localizer runs, 3 in the continuous group, 5 in the intermittent group), where this resulted in activation clusters smaller than 4 voxels, the threshold was lowered to $p < 0.001$ uncorrected. Regions-of-interest were converted to NIfTI format using MarsBaR (version 0.44, Marseille, France (Brett et al., 2002)).

Table 1
Characteristics of tinnitus patients per group.

	Continuous FB group	Intermittent FB group
N	7	7
N (female)	1	2
N (Antidepressants)	1 (Valdoxan)	1 (Cipralex)
N (bilateral tinnitus)	6	5
N (right-sided tinnitus)	0	1
N (left-sided tinnitus)	1	1
Age	46.84 ± 12.01	47.42 ± 12.39
TFI score (initial)	49.43 ± 15.70	49.82 ± 20.28