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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

The feedback signal was calculated from this region-of-interest using a custom-made, real-time fMRI software running on Matlab (Mathworks Inc., Natick, USA, for details see Koush et al., 2012). Online preprocessing included motion correction, extraction of the time courses from the region-of-interest and removal of signal drift, spikes, and high frequency noise. The feedback was presented as the inverted region-of-interest activity by a moving green bar between two fixed points (a white dot on the bottom and a red bar on the top).

Participants were told that this bar reflected how well they are doing (top = good = low region-of-interest activity, bottom = bad = high region-of-interest activity) and that they should try to make the bar rise as high as possible. In order to avoid that the participants feel confused and helpless when presented with this vague task, we did supply them with a list of sample strategies (see Supplementary material). However, we stressed that they were free to change or adapt their strategy as they wished. Subject receiving continuous feedback were informed that the feedback has an intrinsic delay of around 6 s.

All participants underwent three sessions of neurofeedback on three different days. Each day participants performed three neurofeedback runs leading to a total number of nine runs over all sessions. Each run started with 30 s of rest followed by six blocks of neurofeedback and rest. Activity of the 6th to the last second of rest for each rest block was used to establish or update the baseline measure (cumulative average of all baseline measures up to that point). In the continuous group, one block consisted of 40 s of regulation during which the subjects were presented with feedback in form of the moving bar (representing the current inverted activity with respect to the cumulative average across acquired baselines from the 6th to the last second of rest) followed by 20 s of rest. In the intermittent group, 40 s of regulation without feedback (only the instruction to regulate was shown) was followed by 2 s of feedback. Intermittent feedback was calculated as the inverted average activity over second 6–40 of the specific regulation block with respect to the cumulative average across acquired baselines. After the feedback display, a rest period of 18 s finished of each block of the intermittent group. The breathing rate was recorded using Biopac respiration monitoring (RSP100C amplifier, AcqKnowledge version 3.9, Biopac Systems Inc., Goleta, USA). In the last session, subjects underwent one transfer run with the same visual input as during neurofeedback runs but with arbitrary feedback.

2.3. MRI data acquisition

Images were obtained from a 3T Siemens Prisma MRI scanner (Erlangen, Germany) using a 64-channel head coil. All functional images were acquired with a multi-band EPI sequence obtained from the Center for Magnetic Resonance Research of the University of Minnesota (USA, MB factor = 2, TR = 1000 ms, TE = 30 ms, 3 × 3 × 3 mm resolution without gap, 384 × 384 matrix, functional localizer: 280 volumes, neurofeedback & transfer runs: 390 volumes, resting state runs: 360 volumes). An anatomical image (MPRAGE, TR = 2300 ms, TE = 2.27 ms, 1 × 1 × 1 mm resolution, 256 × 256 matrix) was obtained for co-registration with EPI images. Additionally, arterial spin labeling (ASL) images were acquired at the end of the first and last session (FAIR, TR = 4000 ms, TE = 12 ms, TI1 = 600, TI2 = 1600, 3.44 × 3.44 × 4 mm resolution, total of 101 volumes (50 tag, 50 ctrl)).

2.4. Post-hoc GLM and region-of-interest analysis

Post-hoc analysis was performed with FSL (FSL 5.0.6, FMRIB, Oxford, UK). A first level general linear model was used modeling the stimulation periods for the localizer run or regulation periods for the neurofeedback runs. Standard preprocessing was used including motion-correction, spatial normalization and smoothing using a Gaussian kernel at 5 mm FWHM. In addition to the main regressor, motion parameters and the breathing recording were used as co-regressors. In a second-level mixed effects (FLAME1) analysis of all neurofeedback runs, the main effect of regulation was calculated as well as a contrast between the continuous and intermittent group. In order to assess effects between the groups in a meaningful way, we ran four conjunction analyses between the main effect and the between-group effects using "easythresh_conj" by Stephen Smith and Mark Jenkinson (FMRIB, Oxford, UK, Part of FSL - FMRIB's Software Library, $p < 0.05$).

Thresholded images are shown for the whole brain ($p < 0.05$, multiple comparison corrected). For a more detailed view, unthresholded images masked with the target region are shown as well to illustrate how the effects are spatially distributed within the whole target region (see lower row of Figs. 2 and 3).

Additionally, the activity within the individually defined region-of-interest was analysed employing featquery using stats/cope and converting the change to percent signal change (options within featquery, Mumford, 2007). Differences between (i.e., group effect) and within (i.e., session effect) groups were analysed using a repeated-measures ANOVA. In case the ANOVA showed significant results, post-hoc two-tailed paired *t*-tests were conducted between all sessions/groups. To further explore the effect of the exact region-of-interest inside the auditory cortex, this analysis was repeated post-hoc with a region encompassing only parts of the secondary auditory cortex in the Supplementary material. This region was defined as the overlap of the main effect from the second-level GLM deactivation and the localizer activation (see Supplementary material).

2.5. Resting-state analysis

In addition to neurofeedback runs, subjects also completed two resting-state scans of 6 min with eyes closed. The first run was performed at the beginning of the first session while the second run was performed at the beginning of the last session. Functional connectivity analysis was implemented, using the auditory cortex, as defined by the functional localizer run, as a seed region. In a second level analysis, the main effect of sessions (Session 1 versus Session 3) over all subjects was calculated as well as a comparison between the two groups (Continuous feedback versus intermittent feedback).

2.6. Arterial spin labeling analysis

The mean relative cerebral blood flow (relCBF) from the ASL data was automatically calculated by a built-in algorithm in the MR scanner console. These CBF maps were spatially normalized and smoothed using a Gaussian kernel at 5 mm FWHM. We then extracted the mean CBF of the auditory cortex as defined by the functional localizer. In a second level analysis, the main effect over all subjects was calculated as well as a comparison between the two groups.

2.7. Assessment of tinnitus

The tinnitus was assessed by the tinnitus functional index questionnaire (TFI) before, directly after the last session and 6-weeks after the neurofeedback training. The TFI consists of eight sub-scores for different aspects of tinnitus including sense of control, sleep and relaxation. One participant from the continuous group did not return the follow-up questionnaire, even after we sent out several reminders. This participant was therefore excluded from the behavioral analysis. In addition, subjects were asked to rate the subjective loudness and annoyance of the tinnitus on a numerical rating scale from 0 to 10 before and after each neurofeedback run.

Behavioral data was analysed in Matlab using repeated-measures ANOVA with the factors group and time point.

3. Results

3.1. Functional localizer

As expected, the functional localizer reliably identified the auditory cortex as our target region. A group analysis over all subjects shows a bilateral activation in the primary auditory cortex and part of the secondary auditory cortex (see Fig. 1).

3.2. Neurofeedback runs – whole brain analysis

The main effect of neurofeedback runs shows large areas of deactivation during neurofeedback in comparison to rest as well as some activations. Overall, there was a significant deactivation of large parts of the auditory cortex (see Fig. 2). Interestingly, most of the deactivated regions were situated towards the border of the target region (green in Fig. 2), where the secondary auditory cortex is located. The middle of the target region, where the primary auditory cortex is located, was less deactivated. Towards the posterior, medial edge of the target region there is a very small area that is not deactivated but non-significantly activated (see Fig. 2, horizontal view of the lower row). Moreover, there are several additional deactivations, most prominently in the visual cortex. Some activation can be seen in prefrontal regions, the anterior insula, the supplementary motor area and the visual area MT.

When looking at the conjunction analysis of continuous < intermittent feedback and regulation < rest, we can see that in small parts of the target region the continuous group has a stronger deactivation in comparison to the intermittent group (see Fig. 3, none of the other conjunction analyses showed any effect in or near the target region). In addition, the conjunction analysis of continuous > intermittent feedback and regulation > rest shows an increased activation of the higher visual cortex including area MT as well as some parietal and prefrontal regions in the continuous group compared to the intermittent group.

3.3. Neurofeedback runs - region-of-interest analysis

Over all sessions, the average activity of the individual region-of-interest within the auditory cortex (percent signal change in comparison to rest condition) was significantly lower than zero for the continuous group (*t*-test, $p = 0.0046$) while the intermittent group only showed a trend towards down-regulation ($p = 0.057$, see Fig. 4A). However, when comparing both groups directly, there was no significant difference (repeated-measure ANOVA, $F(group) = 1.82$, $p(Group) = 0.19$). Over sessions (see Fig. 4B), there were no significant effects ($F(Session) = 0.77$, $p(session) = 0.47$). There was no significant group x session interaction ($F = 2.11$, $p = 0.13$). The continuous group improved very slightly (i.e. stronger deactivation) on a descriptive level, while the intermittent group became worse to an extent that there is no down-regulation effect at all towards the last session.

As the GLM analysis revealed that the secondary auditory cortex was more modulated than the primary auditory cortex, it would also be interesting to see how this sub-region behaves in comparison to the whole region. Therefore, we performed a post-hoc region-of-interest analysis for the area that overlapped the deactivation of the main effect and the auditory localizer activation. For this area, the continuous group showed even stronger deactivation on average while the intermittent group showed similar results as in the whole target region analysis (see Supplementary Fig. 2).

3.4. Resting-state analysis

Resting-state connectivity revealed no effect of time (Session 1 versus Session 3) when looking at the mixed effects analysis. We subsequently ran a fixed effects analysis for all patients to check for weaker effects that might not be able to reach significance in a mixed effects analysis due to the small sample size. Functional connectivity increased in the posterior cingulate cortex and the premotor area as well as part of the insula (see Fig. 5). It decreased in parts of the parietal lobe. The same analysis for the continuous versus the intermittent group showed only minor changes in a fixed effects analysis (see Supplementary material, Fig. S3).

3.5. ASL analysis

The ASL analysis showed no significant differences of the CBF within the auditory cortex neither between sessions ($p = 0.29$) nor between groups ($p = 0.93$).

3.6. Behavioral analyses

Overall, TFI scores showed a trend towards a difference between pre-, post-test and the six weeks follow-up ($F(Time) = 3.05$, $p = 0.068$). The effect did not show to be significant when looking at the groups individually (continuous group: $p = 0.115$, intermittent group $p = 0.517$) though on a descriptive level there is a slight decrease in TFI score (5 out of 6 showed a decrease between pre-and post-test) in the continuous group that is not present in the intermittent group (4 out of 7 showed a decrease, see Fig. 6). There was no effect of group ($F = 0.02$, $p = 0.92$) and no significant group x time interaction ($F = 1.11$, $p = 0.35$).

When looking at the sub-scores of the TFI, the relaxation score (high = relaxation capacity strongly impacted by tinnitus, low = only marginally impacted by tinnitus) was significantly different between the time points (repeated-measure ANOVA, $F(time) = 5.81$, $p(time) = 0.0094$) when looking at all subjects.

A significant effect was also present when looking at the continuous group only ($p = 0.023$, Fig. 7). Post-hoc testing revealed that this effect was mainly driven by the decrease in score between the pre- and the post-FB session (*t*-test, $p = 0.012$). Additionally, the difference between the pre-FB session and the six weeks follow-up showed a trend towards significance (*t*-test, $p = 0.084$). No significant differences were found for the intermittent group. When looking at the group factor ($F = 0.25$, $p = 0.63$) and the group x time interaction ($F = 2.38$, $p = 0.12$), no significant differences were detected.

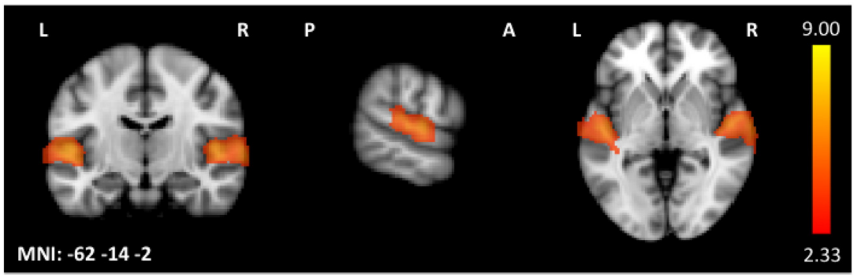

Fig. 1. Main effect of the auditory localizer over all subjects (n = 14, z-values).

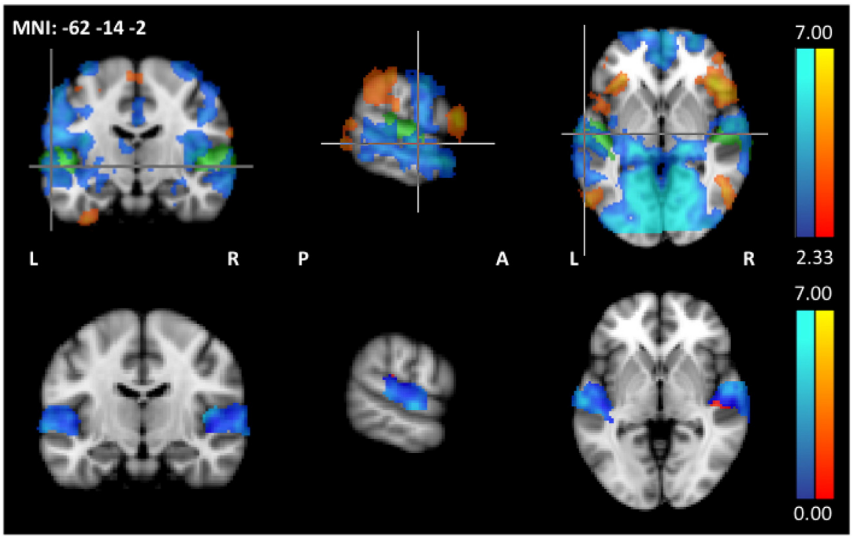

Fig. 2. Main effect of regulation across both groups (n = 14, z-values). The neurofeedback target region (auditory cortex) is displayed in green in the thresholded analysis in the upper row ($p < 0.05$, corrected). Activation during neurofeedback blocks is shown in red to yellow while deactivation is shown in blue. The lower row shows unthresholded results of the target region for illustration purposes.

4. Discussion

Our study demonstrated that continuous feedback seems to perform better than intermittent feedback over multiple sessions when regulating the auditory cortex in a clinical setting. In contrast, intermittent feedback showed the strongest down-regulation effect in the first session. In a GLM analysis, parts of the targeted auditory cortex showed a stronger deactivation in the continuous group in comparison to the intermittent group. Additionally, the TFI scores tended to improve in the continuous group (though not significantly, possibly due to the low sample size) while the scores of the intermittent feedback group remained unchanged. The TFI relaxation sub-score even indicated a significant decrease of the interference of tinnitus with relaxation in the continuous group; i.e., after all neurofeedback sessions, continuous feedback patients could relax significantly better (= decrease in score) than before. It is not surprising that relaxation is the aspect of tinnitus that benefits most as tinnitus is known to be linked to decreased relaxation, especially when tinnitus is accompanied by sleep disturbance, depression or anxiety (Langguth, 2011, Malouff et al., 2011). A biofeedback study demonstrated that targeting increased relaxation can decrease tinnitus severity in some cases (Carmen and Svihovec, 1984). This idea is also supported by the results of a resting-state fMRI study revealing that in tinnitus the connectivity between limbic areas and cortical networks not typically involved with emotion processing is increased (Husain and Schmidt, 2014). Therefore, it seems plausible that by down-regulating the target region, other regions that are increasingly used for (negative) emotion processing in tinnitus may also become less active thereby decreasing tinnitus distress.

A previous study on healthy subjects that were regulating the left premotor cortex (Johnson et al., 2012), demonstrated that intermittent feedback improved regulation in comparison to continuous feedback in a single session design. It is important to realize that neurofeedback regulation is a cognitively challenging task, as witnessed by the involvement of a widespread neuronal network for the regulation process per

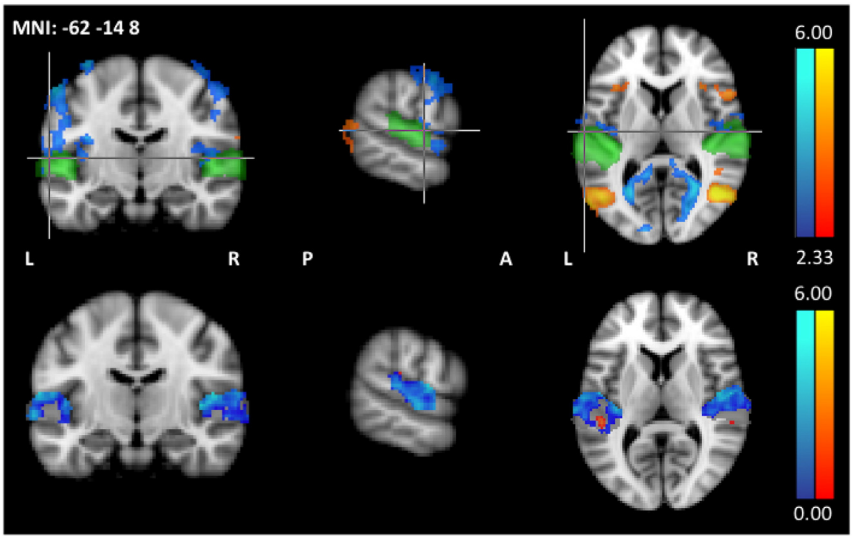

Fig. 3. Conjunction analyses of the continuous versus intermittent FB group of the regulation effect (z-values). The neurofeedback target region (auditory cortex) is displayed in green in the thresholded analysis in the upper row ($p < 0.05$, corrected). Red to yellow regions show stronger activation during neurofeedback for the continuous in comparison to the intermittent group. Blue areas indicate regions that show a stronger deactivation during neurofeedback for the continuous in comparison to the intermittent group. The lower row shows unthresholded results of the target region for illustration purposes.

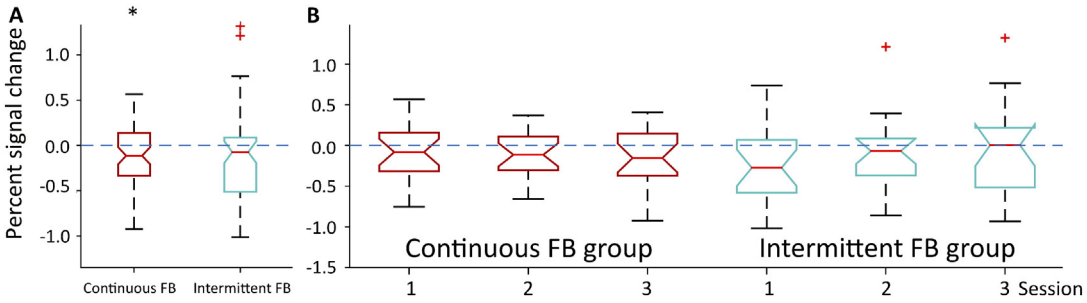

Fig. 4. Boxplots of target region signal change during regulation for the continuous FB group (red) and the intermittent FB group (turquoise). A: over all sessions, B: per session. The asterisk indicates significance ($p < 0.05$).

se (Emmert et al., 2016). Performing such a challenging task in a novel environment of a MR scanner may initially be difficult, and consequently it is plausible that for the first day the intermittent feedback may be easier as it does not require the participants to continuously monitor the feedback signal while trying to find a successful regulation strategy. In line with this argument, when looking only at the first neurofeedback session, intermittent feedback seemed to show a stronger down-regulation tendency than continuous feedback (see region of interest analysis).

However, over time the participants get used to the environment and the task and can better focus on the feedback processing. Correspondingly, at days two and three, the continuous feedback group was apparently able to benefit from the fine-grained and more detailed neurofeedback information and improved slightly (but not significantly) over time, while the intermittent feedback group with the less detailed and delayed feedback did not further improve and actually even got worse, which is probably due to frustration and consequently less attention to the task. In summary, our results indicate that the more detailed feedback information in continuous feedback had a slightly negative effect for the initial period – in agreement with the previous study (Johnson et al., 2012). However, in the long run, continuous feedback provides more details to the participants and consequently had better regulation success in later sessions, and may therefore be recommended for some clinical applications, like tinnitus. Additional differences between the study by (Johnson et al., 2012) and the current investigation are that in Johnson et al. participants were trained to regulate a motor area and therefore had a very straightforward strategy (i.e., motor imagery), which was not the case for auditory down-regulation. Auditory down-regulation might rely more on implicit learning, which is facilitated if feedback is provided more directly as is the case with continuous feedback. Moreover, the choice of participants (healthy subjects (average age 31.6 years) versus tinnitus patients (average age 47.1 years)) may impact the effectiveness of both feedback presentation types as well.

The regulation effect seems to be more pronounced in parts of the secondary auditory cortex. This indicates that parts of the secondary auditory cortex may be more susceptible to voluntary modulation in comparison to the primary cortex (Diamond and Weinberger, 1984, Puckett et al., 2007, Cohen et al., 2012). One animal study even suggests that tinnitus may be a consequence of an increased spontaneous firing rate in the secondary but not primary auditory cortex (Eggermont and Kenmochi, 1998). If this is true, it is unsurprising that most of the modulation also happens in this affected brain area. Moreover, there is a very small area within the target region that shows slight up-regulation in contrast to the rest of the region, which may impair the regulation efficiency. Therefore, it would be useful to have a more fine-grained target region selection in future auditory cortex regulation studies to select regions that are easily self-regulated. To this aim, it would also be useful to get a better idea of the spread of tinnitus-associated hyperactivation within the auditory cortex in humans. Ideally, a map of hyperactivation hotspots within the auditory cortex could help improve the target region selection.

Concerning resting-state fMRI results, our study showed a slight increase in functional connectivity in the posterior cingulate cortex, premotor area and part of the insula and a decrease in parts of the parietal lobe between the first and the last session. The increase in connectivity of the insula can be expected, as the insula is known to be involved in a wide variety of cognitive processes including interoception (Craig, 2002, Critchley et al., 2004, Gasquoine, 2014). It has even been identified as one of the central regions involved in neurofeedback regulation in general (Emmert et al., 2016). Posterior cingulate involvement indicates that connectivity between the auditory cortex and the default mode network is increased by neurofeedback training. This fits in line with another study showing increased reactivation of the ventral posterior cingulate cortex after self-regulation with increased regulation strength (Van De Ville et al., 2012, Haller et al., 2013). It should be noted that the specificity of these effects cannot be determined with this analysis due to the absence of a control group.

No significant changes in cerebral blood flow were detected between the first and the last session or between groups using ASL. This indicates that neurofeedback induced changes seem to be primarily caused by changes in the neural activation pattern and not by blood flow per se.

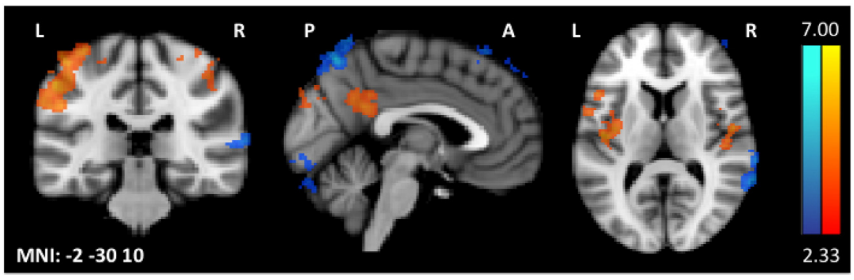

Fig. 5. Effect of session using seed-based connectivity of the auditory cortex (fixed effects analysis, z-values). Orange areas show an increased connectivity in the last compared to the first session. Blue areas show a decreased connectivity in the last compared to the first session.

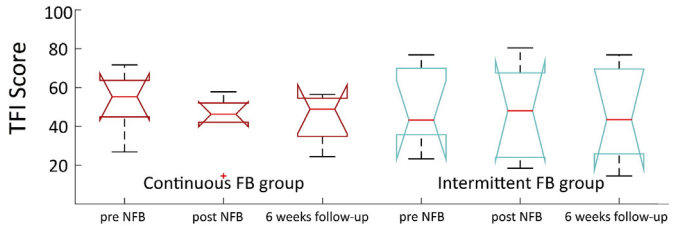

Fig. 6. Boxplots of TFI scores for the continuous FB group (red) and the intermittent FB group (turquoise).

4.1. Limitations

Due to the time-consuming nature of this experiment including three separate sessions, the amount of participants was limited (2 groups with 7 patients each). It is known that neurofeedback is subject to great inter-individual variations (Robineau et al., 2014, Kopel et al., 2016). Therefore, it may well be that we missed a behavioral effect e.g. on the total TFI score due to low statistical power. The same is true for any effect over sessions. Due to the low number of subjects and relatively low number of sessions, neither the slight trend towards improvement in the continuous group nor the decreased regulation trend in the intermittent group were significant. As other real-time fMRI studies often show improvement over time, it is likely that in this case, where patients were asked to down-regulate an area without one straight-forward regulation strategy, the optimal performance was not yet reached. Therefore, a follow-up study with more regulation sessions should aim to confirm the presented results. It should be noted that further experiments including a blinded control group are needed, to determine the overall effect of neurofeedback on tinnitus patients.

5. Conclusion

In conclusion, our study indicates that for self-regulation of a sensory brain region, notably the auditory cortex in tinnitus patients, continuous feedback may be more advantageous than intermittent feedback on the long term while intermittent feedback seems to be well-suited to short neurofeedback experiments. In addition, auditory down-regulation is accompanied by an increased relaxation ability for tinnitus patients when continuous feedback is used. These alterations seem to be caused by actual changes in neuronal activation rather than changes in cerebral blood flow as indicated by our ASL results.

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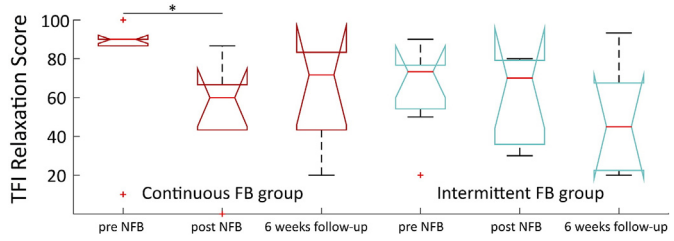

Fig. 7. Boxplots of relaxation scores for the continuous FB group (red) and the intermittent FB group (turquoise). The asterisk indicates significance ($p < 0.05$).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.12.023.

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