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IMPROVEMENT OF REAL-TIME FMRI NEUROFEEDBACK FOR CLINICAL APPLICATIONS

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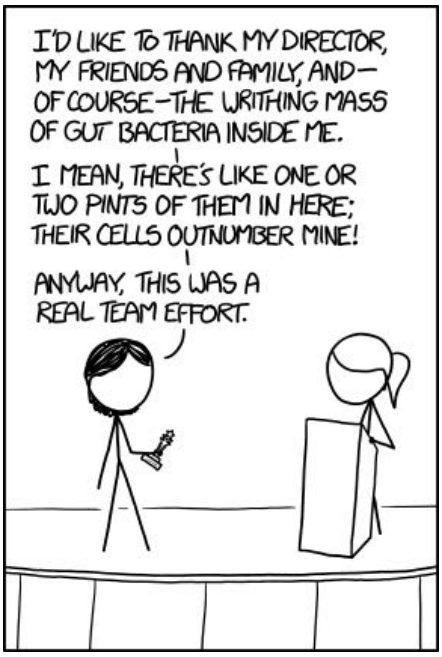

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Abstract

Real-time functional magnetic resonance imaging (fMRI) neurofeedback is an emerging technique that allows participants to gain voluntary control over brain activation.The brain area or network of interest is first localized; then, an fMRI measure of its activity is used as a real-time feedback signal for the participant. Over time, participants learn to influence this activity and thus are able to self-regulate their brain activity. Initial studies demonstrated the feasibility of self-regulation using real-time fMRI and showed that it can influence behaviour as well. Recent studies, therefore, focussed on potential clinical applications. The hope is, that by regulating affected brain areas in a way that the activity approaches that of the normal, healthy population, the course of the disease might be positively affected. However, in order to attain a behavioural or clinical effect, it is necessary that induced self-regulation is strong and stable. Therefore, the goal of this PhD work is to advance the knowledge of clinical real-time fMRI neurofeedback in order to optimise the setup.

To this aim, I address four important open issues in fMRI neurofeedback in this thesis. Firstly, it is unknown which brain areas mediate self-regulation of a target area. This core network of areas should be active in all neurofeedback tasks, independent of the area that is regulated. Secondly, the choice of target region impacts the available strategies for regulation and the success. Therefore, I compare two different target regions of the pain-sensitive network in terms of regulation efficacy. Another open question is how personality traits and habits influence neurofeedback success. In a follow-up study, I therefore assessed personal coping habits as a model for a personality trait relevant in the context of pain neurofeedback. Finally, in the last study I explore different feedback presentation timings to identify the best procedure by comparing between continuously presented and intermittently (after each regulation period) feedback.

The first study, a meta-analysis of individual participant data from several peer-reviewed, international publications, revealed a large regulation network, including the anterior insula, anterior cingulate cortex and the basal ganglia. This network is of major importance when choosing future target brain areas. The second study looked at down-regulation of two different pain-sensitive areas during painful stimulation. The study revealed similar success rates for both tested brain regions, although one of them seemed to influence other nodes of the pain-sensitive network more strongly. Therefore, target region selection should carefully evaluate the role of different brain regions in the targeted network and its connectivity to other regions in order to decide, which would be the most promising target. The follow-up study showed that in particular active coping (i.e. does the participant actively try to cope with the pain, e.g. by positive self-talk or trying to distract her- or himself) is correlated to pain regulation success. This indicates that personality traits or habits may indeed influence regulation success. Finally, the last study looked at down-regulation of the auditory cortex in tinnitus patients. It showed that continuous presentation is superior to intermittent feedback presentation in a clinical setup (clinical population, several neurofeedback sessions) if the target regulation is not associated to a clear prior strategy.

In conclusion, I address several current issues of real-time fMRI neurofeedback in my thesis. These results may serve as a basis to optimise future real-time fMRI studies, notably in a clinical context. They indicate that a careful target region selection, pre-selecting or pre-training participants based on behavioural factors and improving feedback presentation timing may increase regulation strength and clinical efficacy. Thereby, the results of this PhD work may help to advance neurofeedback towards the use as a supplementary treatment for many brain disorders.

Keywords: functional magnetic resonance imaging, neurofeedback, self-regulation, tinnitus, pain

Résumé

Le neurofeedback en temps réel d'imagerie par résonance magnétique fonctionnelle (IRMf) est une procédure expérimentale permettant aux participants de gagner un contrôle volontaire sur l'activation d'une région, ou d'un réseau, de leur cerveau. La région ou le réseau d'intérêt est tout d'abord localisé(e), avant que son activité ne soit mesurée par IRMf, puis transmise au participant en temps réel. Au fur et à mesure des sessions, les participants apprennent à influencer cette activité, et deviennent ainsi capables d'auto-réguler l'activité de leur cerveau. Des études initiales ont montré que l'auto-régulation par IRMf est possible, et que cette régulation influence également des variables comportementales. De nombreuses études récentes se sont ainsi penchées sur de possibles applications cliniques, avec l'espoir qu'en régulant des régions détériorées de sorte que leur activité approche celle d'individus sains, la progression de la maladie puisse être positivement modifiée. Cependant, afin d'atteindre un effet comportemental, il est nécessaire que l'auto-régulation soit forte et stable. Ainsi, l'objectif de ce travail de doctorat est d'améliorer notre connaissance du neurofeedback en temps réel d'IRMf dans un cadre clinique, afin d'en optimiser les diverses facettes.

Dans ce but, je me penche sur quatre questions ouvertes essentielles au neurofeedback d'IRMf. Premièrement, les processus neuronaux prenant place lors du neurofeedback sont pour l'heure inconnus. Plusieurs régions du cerveau devraient médier l'auto-régulation d'une région cible, et ce réseau central devrait être actif dans toutes les tâches de neurofeedback, indépendamment de la région régulée. Deuxièmement, le choix de la région cible a évidemment un impact majeur sur les stratégies utilisées pour la régulation, ainsi que sur son succès. Dans cette optique, je compare ici deux régions cibles du réseau sensible à la douleur. Dans une étude suivie, j'examine ensuite comment le succès de la régulation dans cette tâche est lié à la manière avec laquelle les participants font face à la douleur au quotidien. C'est une question intéressante, car jusqu'à présent l'influence des traits de personnalité et des habitudes sur le succès du neurofeedback n'a jamais été pris en compte. Dans la dernière étude présentée, je cherche à déterminer une présentation de feedback optimale dans un

cadre clinique (les patients souffrant d'acouphènes), en comparant une visualisation en continu avec un affichage par intermittence faisant suite à chaque période de régulation.

Une méta-analyse de données de participants individuels provenant de plusieurs études publiées a révélé un large réseau de neurofeedback incluant l'insula antérieure, le cortex cingulaire antérieur et les ganglions de la base. Ce réseau devrait être précautionneusement considéré pour le choix de futures régions cibles. La deuxième étude présentée a révélé des taux de succès similaires pour les deux régions du cerveau testées, bien que l'une d'elle a semblé influencer les autres nœuds du réseau de la douleur plus fortement. Ainsi, le choix d'une région cible devrait impliquer une évaluation précise de son rôle dans le réseau ciblé, ainsi que de sa connectivité à d'autres régions, pour décider de la cible la plus prometteuse. L'étude suivie a montré qu'en particulier, les stratégies actives mises en place pour s'acquitter de la douleur (par exemple lorsque le participant essaie de se distraire ou de s'encourager) corrélent positivement avec le succès de sa régulation, mettant donc en avant un impact notable des traits de personnalité et des habitudes. Finalement, la dernière étude a montré que le feedback continu est supérieur à une présentation intermittente dans un cadre clinique (populations cliniques, plusieurs sessions de neurofeedback) si la régulation de la région cible n'est pas associée à une stratégie préalable claire.

En conclusion, j'explore dans ma thèse plusieurs points d'intérêt actuels du neurofeedback en temps réel d'IRMf. Au vu des résultats, de futures études devraient optimiser leur mise en place en ajustant le choix de la région cible, en présélectionnant ou en entraînant au préalable les participants selon des facteurs comportementaux, et en perfectionnant le timing de la présentation du feedback. Améliorer ainsi le neurofeedback en temps réel d'IRMf pourrait augmenter la force de régulation et l'efficacité clinique, aidant ainsi à propulser le neurofeedback vers un rôle de traitement supplémentaire pour de nombreuses pathologies du cerveau.

Mots-clés : imagerie par résonance magnétique fonctionnelle, neurofeedback, auto-régulation, acouphène, douleur

Contents

Introduction

The overarching research theme of this PhD dissertation is to improve neurofeedback (NFB) techniques based on real-time functional magnetic resonance imaging (fMRI). In this emerging approach, the MRI scanner is not only used for imaging, but also for intervention by providing feedback about brain activity to the participant who can then subsequently learn to regulate it.

This dissertation consists of three main experiments. The first one uses several existing datasets of NFB in healthy participants in order to determine common regulation effects during NFB. The second experiment uses NFB during painful heat stimulation in healthy subjects. This dataset includes meta-data on subjective pain perception and coping and is used to compare NFB efficacy of different target regions and the influence of individual behavioural factors on NFB success. Finally, the last dataset uses a clinical population, namely tinnitus subjects, to determine the best timing of neurofeedback presentation.

In sum, these experiments will help to advance target region selection and setup configuration of NFB studies, thus making neurofeedback more efficient for its use in clinical populations. In the following chapters I will try to give an overview of the state-of-the-art of real-time fMRI neurofeedback and current issues in the field. Afterwards, I will give a short introduction to two fields of application for neurofeedback: pain and tinnitus. After presenting the pathophysiology of both pain and tinnitus as well as structural and functional brain changes associated with it, I will then propose which of these changes might be best targeted by real-time fMRI NFB.

1.1 Bio- and Neurofeedback

The idea of using feedback from bodily functions to learn to control them is a well-established concept. A variety of feedback modalities have been employed since its beginnings in the 1960s such as body temperature, heart rate and its variability, sweat gland activity and blood volume as well as electroencephalogram (EEG) and electromyography (EMG) measures. Targeted disorders include migraine and tension headache [1, 2], muscle weakness [3, 4], chronic pain [5, 6], cardiac [7, 8], gastrointestinal [9–11] and mental disorders [12–15].

Biofeedback that tries to influence brain function is called neurofeedback. In animal studies it was shown that non-human primates and rats are able to gain specific control over single-cell firing within the motor cortex [16–18].

The most prominent modality for neurofeedback in humans is EEG where participants try to control electrical brain activity in real-time. EEG NFB targets either spectral power, event-related potentials or slow cortical potentials [19]. Most commonly a certain spectral power band is trained to be either increased or decreased or the ratio between two power bands is targeted. Common EEG NFB measures include the sensory motor rhythm (SMR) (12-15 Hz) band, the ratio of SMR in comparison to frequencies outside the considered bandwidth, upper-alpha (10-12 Hz), alpha desynchronisation, beta1 (13-19 Hz), beta1 ratio, gamma (36-44 Hz) and gamma ratio, theta (4-7 Hz) and alpha/theta ratio [19].

EEG NFB is used to enhance performance in healthy subjects as well as to help restore function in clinical populations. Performance enhancement includes cognitive and sports performance increase [19]. Considering clinical application, EEG NFB has been employed for example in the domains of attention deficit hyperactivity disorder (ADHD) [20], epilepsy [21], tinnitus [22], addiction [23–25], stroke recovery [26, 27], anxiety [23, 28] and depression [23, 29] as well as insomnia [30, 31].

Most research has been conducted in the domain of ADHD, where initial clinical trials showed promising results [32]. However, more recent blinded studies were not able to confirm the efficacy of EEG NFB in ADHD patients [20]. Therefore, further work on improving the method and additional double-blind studies with careful participant selection are needed to evaluate EEG NFB as a complementary therapeutic tool [33].

Alternative neurofeedback modalities include magnetoencephalography (MEG), functional near infrared spectroscopy (fNIRS), transcranial doppler sonography [34] and fMRI [35].

1.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging assesses the change of the blood oxygen level dependent (BOLD) contrast during neuronal activity. Increased neuronal activity impacts local blood flow and oxygen consumption, so that the proportion of deoxygenated and oxygenated blood in the involved region changes. As deoxygenated and oxygenated blood have different magnetic properties [36], it is thus possible to detect increased neuronal activity indirectly. Ogawa et al. were the first to prove that an increase in blood flow changed the BOLD contrast [37].

During neuronal activity, local blood flow increases, so that more oxygenated blood is supplied to the active region [38]. In parallel, oxygen consumption and glucose use also increase. Overall, the rise in oxygenated blood due to a stronger local cerebral blood flow is greater than the increase in oxygen consumption [39]. Therefore, the net amount of oxygenated blood increases locally, leading to a transient increase in magnetic resonance (MR) signal that can be detected. The indirect detection of increased local brain activity following sensory stimulation using magnetic resonance imaging (MRI) was demonstrated soon after the detection of this mechanism [40–42]. However, the exact nature of the relationship between neural activity and the BOLD signal is still not completely clear. Some studies suggest that the BOLD signal may be linked to either spiking activity [43], local field potentials [39, 44, 45] or both [46]. Logothetis notes that the BOLD contrast will reflect changes in the excitation-inhibition balance but that "without understanding the intrinsic correlation between direct or indirect inhibitory activity and concomitant changes in energy metabolism in a given situation, conclusions cannot be drawn" [47].

However, the time-course of the brain-activity induced BOLD response is well studied. The hemodynamic response to increased neural activity starts with an initial dip of around one to two seconds; this typically results from an initial increase in the rate of deoxygenated blood caused by an unmet increase in oxygen demand [48, 49]. Subsequently, local blood flow increases to an amount that overcompensates for the previous lack of oxgenated blood, leading to a net increase in oxgenated blood with a peak at around five to six seconds after neural activity onset [48]. After the end

of neural activity the blood flow initially decreases to a greater extent than blood volume, leading to an overall increased amount of deoxgenated blood. Therefore, the BOLD signal decreases below baseline (undershoot) for some seconds before recovering.

For a standard fMRI design, blocks of stimulation are contrasted against rest periods (block design), which is an efficient way to uncover the differences between conditions. In addition, it is also possible to detect shorter events in a less stringent arrangement, but this requires a careful design of the timing [50]. For NFB purposes, a very cognitively demanding task, block design is usually preferred to allow subjects to immerse themselves into the task for a certain time.

1.3 Real-time fMRI

Real-time fMRI NFB uses real-time processing of fMRI data to give subjects feedback about the brain acitivity of a certain region or network while they are inside the MRI scanner. This way, the technique allows voluntary control over the selected brain region or network [51]. In comparison to EEG NFB, which offers a good temporal resolution, fMRI NFB exhibits a better spatial resolution and includes the possibility to reach subcortical regions. After its technical development in the 2000s using healthy participants, nowadays it is increasingly used in clinical populations.

1.3.1 Real-time fMRI neurofeedback in healthy participants

fMRI neurofeedback uses the BOLD contrast to indirectly calculate brain activity in near-real-time. Great advancements in the methods development of fMRI in the 1990s resulted in the possibility to process and look at fMRI data in real-time [52]. In the early 2000s, the first proof-of-concept studies then targeted simple, sensory brain regulation to show the feasibility of fMRI neurofeedback in healthy subjects. Yoo et al. were the first to show that visual presentation of sensory and motor cortex activation during a motor task could help to adjust the subject's strategy to achieve a more widespread activation [53]. Over the last years this concept has been refined and applied to a range of target regions. For an overview over all areas that have been used for regular fMRI NFB please see Table 2.1 and Figure 1.1.

Area	Initial Studies	Regulation	Participants/ Comments
Amygdala	Posse et al. 2003 [54]	Up	Healthy Participants
Anterior Cingulate Cortex	Weiskopf et al. 2003, DeCharms et al. 2005 [55, 56]	Up/Down	Partly Chronic Pain Patients [56]
Anterior Insula	Caria et al. 2007 [57]	Up	Healthy Participants
Auditory Cortex	Haller et al. 2010 [58]	Down	Tinnitus Patients
Dorsolateral PFC	Zhang et al. 2013, Sherwood et al. 2016 [59, 60]	Up	Healthy Participants
Inferior Frontal Gyrus	Rota et al. 2009 [61]	Up	Healthy Participants
Parahippocampal Cortex (PPA)	Weiskopf et al. 2004 [62]	Up(in comparison to SMA)	Healthy Participants
Posterior Cingulate Cortex	Garrison et al. 2013 [63]	Down	Meditators
Posterior Insula	Rance et al. 2014 [64]	Up and Down	Healthy Participants (+pain)
Primary Motor and somatosensory cortex	Yoo et al. 2002, 2004, DeCharms et al. 2004 [53, 65, 66]	Up	Healthy Participants
Substantia Nigra/Ventral Tegmental Area	Sulzer et al. 2013 [51]	Up	Healthy Participants
Superior Frontal Gyrus	Yoo et al. 2004 [66]	Up	Healthy Participants
Supplementary Motor Area (SMA)	Weiskopf et al. 2004 [62]	Up (in comparison to PPA)	Healthy Participants
Ventral Striatum	Kirsch et al. 2015 [67]	Down	Heavy Drinkers

Visual Cortex	Shibata et al. 2011, Scharnowski et al. 2012 [68, 69]	Likelihood of pattern up/ Up	Healthy Participants

Table 1.1 – Regions of interest that have been targeted with real-time fMRI (without connectivity NFB)

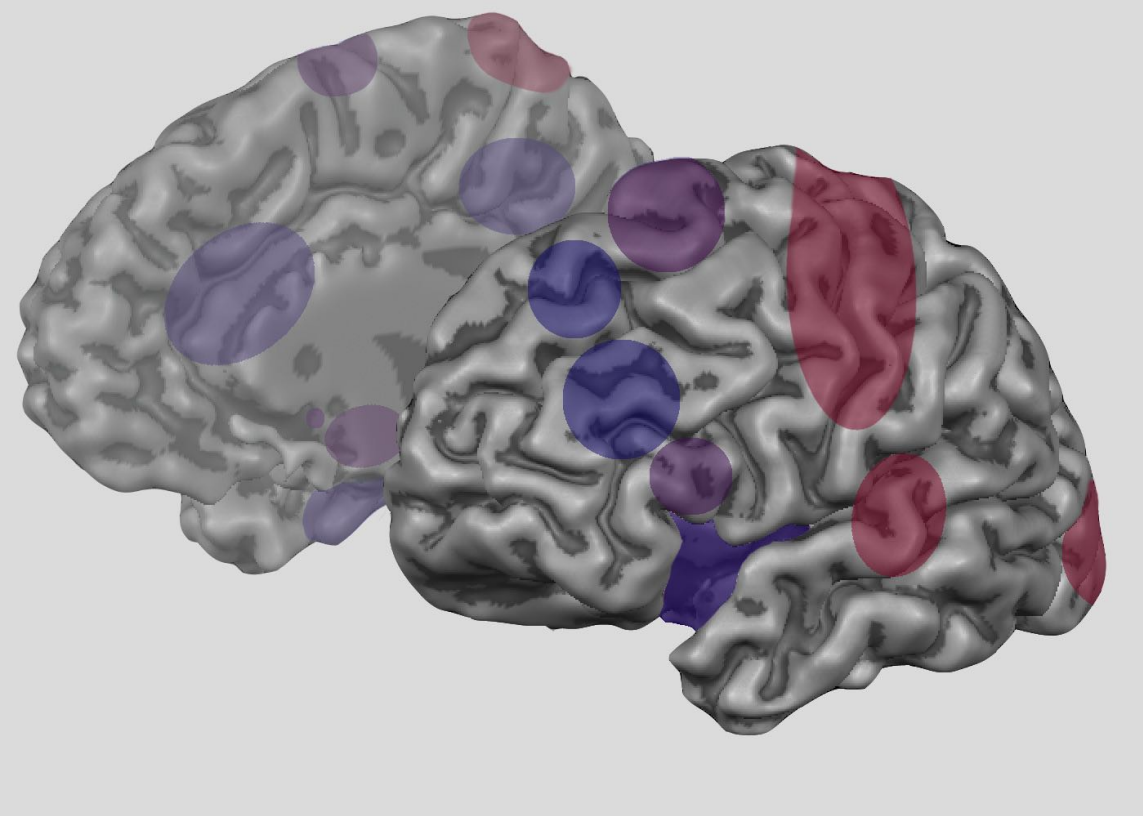

Figure 1.1 – High-level (=blue) and low-level (=red) target areas for real-time fMRI neurofeedback. Posterior insula and substantia nigra / ventral tegmental area are not displayed.

As most brain functions rely on a network of specific brain areas and on their interactions, in recent years researchers have been trying to improve fMRI NFB by

providing measures of connectivity. The pioneering study employed dynamic causal modelling to look at the relationship between right visual cortex - parietal cortex connectivity and left visual cortex - parietal cortex connectivity [70]. In addition, sliding window correlation was proposed as another suitable connectivity measure for fMRI NFB [71]. In a pilot study with smokers it was demonstrated that feedback that included a correlation-based signal yielded better behavioural results than normal fMRI NFB [72]. Other studies with healthy participants also showed success in using correlation-based feedback [73] and intermittent correlation-based feedback [74] for brain regulation. Recently, a sliding window correlation approach gave promising results regulating cortico-thalamic connectivity in stroke patients [74].

1.3.2 Clinical applications of real-time fMRI neurofeedback

After the feasibility of real-time fMRI NFB was demonstrated, one focus moved towards clinical application. The first clinical applications where fMRI NFB indicated beneficial effects include chronic pain [56], tinnitus [58] and Parkinson's Disease [75]. Since then, several pilot-studies for a variety of psychological and somatic diseases have been performed with promising results. For an overview of all studies on clinical populations please see Table 1.2. NFB studies about pain and tinnitus are described further in the following chapters (1.4 and 1.5).

Disorder	Study	Brain Region	N Patients/ Controls
Alcohol Addiction	Karch et al. 2015 [76]	Alcohol cue sensitive (ACC, DLPFC,IC)	13/2
	Kirsch et al. 2015 [67]	Ventral Striatum	13/13
Anxiety (spiderphobia)	Zilverstand et al. 2015 [77]	IC and DLPFC	9/9
Chronic Pain	deCharms et al. 2005 [56]	ACC	12/36
	Guan et al. 2015 [78]	rostral ACC	6/8
Chronic Stroke	Sitaram et al. 2012 [79]	Ventral Premotor Cortex	2/0
	Liew et al. 2015 [74]	Connectivity between M1 and ipsilateral thalamus	4/0
Chronic Tinnitus	Haller et al. 2010 [58]	Auditory Cortex	6/0

Depression	Linden et al. 2012 [80]	Emotion regulation sensitive (VLPFC, IC, DLPFC, MTL, PFC)	8/8
	Young et al. 2014 [81]	Amygdala (L)	14/7
	Yuan et al. 2014 [82]	Amygdala (L)	27/27
	Schnyer et al. 2015 [83]	multivariate pattern analysis (closed-loop FB)	7/0
Nicotine Addiction	Li et al. 2013 [84]	ACC, medial PFC	10/0
	Canterberry et al. 2013 [85]	ACC	9/0
	Hanlon et al. 2013 [86]	Nicotine cue sensitive within PFC	15/0
	Kim et al. 2015 [72]	Group1: ACC, medial PFC and OFC, Group2: as group 1 but combined with connectivity information of this ROI to PCC and Precuneus	14(7 vs 7)/0
OCD	Scheinost et al. 2014 [87]	OFC/ anterior PFC	5/0
	Buyukturkoglu et al. 2015 [88]	anterior IC	3/0
	Hartwell et al. 2016 [89]	Nicotine cue sensitive within PFC	21/23
Parkinson's Disease	Subramanian et al. 2011 [75]	Supplementary Motor Complex	5/5
Psychopathy (with criminal record)	Sitaram et al. 2014 [90]	Anterior IC	4/0
Schizophrenia	Ruiz et al. 2013 [91]	IC	9/0
	Cordes et al. 2015 [92]	ACC	11/0
	Dyck et al. 2016 [93]	ACC	3/0

Table 1.2 – Studies about clinical applications of real-time fMRI.

Abbreviations used in Table 1.2: ACC=anterior cingulate cortex, PCC= posterior cingulate cortex, DLPFC=dorsolateral prefrontal cortex, VLPFC=ventrolateral prefrontal cortex, OFC=orbitofrontal cortex, MTL=medial temporal lobe, IC=insular cortex, M1=primary motor cortex.

1.3.3 Neural plasticity induced by real-time fMRI neurofeedback

Apart from the short-term goal of controlling the target region, neurofeedback ultimately aims at optimising function and structure of the whole brain. There are some studies that showed that neurofeedback induces neural plasticity. An EEG study showed that fractional anisotropy of white matter tracts implicated in sustained attention increased [94] after neurofeedback. In parallel, the grey matter volume within the attention network also increased. A real-time fMRI study showed functional connectivity changes induced by neurofeedback as well [95]. In addition, recently, a theory explaining EEG neurofeedback effects has been put forward. According to this theory, neurofeedback helps to tune brain function toward a homeostatic set-point that provides the best balance between network flexibility and stability [96].

1.3.4 Learning mechanisms in real-time fMRI neurofeedback

FMRI NFB learning is often seen as operant learning of the BOLD response [97]. By receiving proportional reinforcement of the regulation of brain activation (the stronger the regulation in the correct direction, the stronger the reinforcement), participants learn to control their brain activation. Operant conditioning was shown to be successful when trying to train direct control over neural activity in animals [16, 98]. In addition, this learning model is used in the EEG NFB literature, marking operant conditioning as the main learning mechanism [99].

However, this model does not take into consideration the use of explicit strategies, which participants nonetheless describe using frequently during NFB. One frequently used strategy for different target regions is mental imagery. A few studies even suggest that the use of mental imagery is linked to the regulation success [97, 100–102]. However, other studies demonstrate that the feedback signal is essential for regulation learning and that mental imagery alone is not enough to lead to successful regulation [69, 97, 103, 104]. This has also been noted to be true for EEG NFB [105], where

learning might be explained by a two-process theory according to Lacroix [106]. In the initial phase, certain behaviours from within the subjects repertoire are amplified when they are met with positive feedback. This may include the increasing use of a certain explicit strategy. Only in a second phase is the feedback then associated with the interoceptive stimuli [105] .

In addition, neurofeedback learning may also encompass skill learning. In skill learning, there is supposed to be an initial phase of strong performance improvement linked to changes in the dorsomedial striatum followed by a late phase with slower, gradual enhancement correlated with dorsolateral striatum changes [107, 108].

1.3.5 Regions involved in self-regulation

To further advance neurofeedback, it will be important to identify the regions that are involved in the neurofeedback process per se and differentiate their activation from the regulation effects. As most studies target only one region or function, they do not allow to distinguish between these different processes. One network that is likely to be activated during neurofeedback is the central executive network consisting of the dorsolateral prefrontal cortex and the posterior parietal cortex [109]. Moreover, neurofeedback may likely activate the saliency network including the anterior cingulate cortex and the anterior insula [110]. Furthermore, the feedback presentation itself will also evoke activation within the according sensory cortices i.e. usually activation within the occipital cortex for visual feedback presentation.

In addition, strategy-specific activations will also contribute to the active regions during neurofeedback. As many studies use mental imagery, higher-order visual areas may be active during these neurofeedback blocks [111, 112]. In the same manner, imagination of action may lead to activation of the premotor areas [113, 114].

A recent study looking at the implications of neurofeedback success on brain activation found that success correlated with later deactivation of the medial prefrontal and anterior cingulate cortices, while failure to regulate correlated with early-phase deactivation in the precuneus and posterior cingulate cortex [115].

1.3.6 Challenges of real-time fMRI neurofeedback

Despite the great development of real-time fMRI NFB within the last decade, there are still a number of challenges that remain in order to optimise the setup, prove its

efficacy in clinical trials and determine the right target population that benefits most from NFB .

1.3.6.1 Online computation and presentation of feedback

The feedback signal usually represents the motion-corrected signal from one area or the differential feedback of one area in comparison to a control region [57]. The differential feedback has the advantage of cancelling out physiological noise, such as breathing or pulse artefacts, which have been shown to impact the BOLD signal [116–118]. However, non-physiological noise would be amplified by this procedure, thereby reducing the signal-to-noise ratio.

Concerning the presentation of the feedback, the standard is a thermometer-like display of the feedback that is updated with every acquisition time point. Sometimes the activation is also displayed as a colour from a colour range (e.g. from blue=low to yellow=high) [119] or the colour and position are combined as feedback information [51]. Other simple visual representations include a burning fire [56] and facial expressions [120]. Additionally, virtual reality [121] or the integration of the feedback in a computer-game [122] have also been used as feedback modalities. Some studies used a closed-loop system where the feedback in turn regulates the salience of the stimulus. Salience has been manipulated for example by picture size [123] or opacity [72]. In addition to visual feedback, one could also imagine using auditory, tactile or even olfactory cues. So far, only auditory feedback has been explored in a successful pilot study [54].

Continuous feedback presentation might interfere with the subjects efforts to focus on the regulation. However, in order for intermittent feedback, once after each block, to work, participants have to maintain a more or less stable regulation throughout the whole block. One study looking at this issue targeting the premotor cortex indicates that intermittent feedback might be superior to continuous feedback [124].

1.3.6.2 Participant instructions in neurofeedback studies

Due to the unresolved issues concerning the learning mechanism of NFB, it is not clear in what way subjects should be instructed. On the one hand, providing strategy suggestions limits the subject to a small subset of very explicit strategies. On the other hand, MRI scanner time is limited due to financial restrictions, so if the only instruction is to control the feedback a big part of the participants may not arrive at a stage where they can control the feedback in time without some hints about possible

strategies. While some studies favour an explicit strategy [56, 57], others showed fast regulation learning without providing any strategy [68, 125]. One study comparing between participants that were offered an explicit strategy and those who were not, found no significant difference between the two groups when self-regulating a motor area [126]. Additionally, the best approach may vary depending on the targeted brain function or area and whether there are explicit strategies associated with it, as for example when looking at primary sensory areas.

1.3.6.3 Blinding of neurofeedback studies

In order to move from successful pilot studies to clinical trials with randomised, double-blind, controlled studies, it is essential to have a valid placebo group. At the moment, this is an ongoing challenge in the field of fMRI NFB. Most studies that include a control group use feedback from previous participants or artificial feedback as sham condition [61, 67, 103]. The disadvantage of this and of most other approaches is that as participants' action and reward are uncoupled, frustration may be induced more easily than in the real NFB condition [125]. Sham feedback can also be provided from a non-target area [56, 69], leading to a dependence between the test subject's action and the feedback. However, subjects might learn to regulate the control region to some degree which would confound the comparison between the two groups. Choosing a task-negative area such as a node from the default-mode network might prevent this but would most likely lead to a discouraging feedback. The same is true for a sham condition in which the feedback is simply inverted [51]. Moreover, depending on the targeted brain function or area, there might be no gold standard in terms of positive effects that the neurofeedback can be compared with.

1.3.6.4 Feasibility for populations with special needs

Due to the high cognitive demand of neurofeedback, the question remains how well real-time fMRI neurofeedback is suited to clinical populations, children and elderly. A recent study in children and adolescents (7-17 years old) found that they successfully learned to regulate the insula [127]. Similarly, pilot studies with severely impaired clinical participants such as stroke patients showed promising results in most cases [74, 79]. Understandably, patients often show increased intrinsic motivation in comparison to young, healthy volunteers, which might be one reason why they have comparable success rates despite lower overall cognitive performance. However, due to the very small sample sizes, future studies are needed to verify these results. To date, no studies looking at elderly participants in particular have been reported.

1.3.6.5 Variability of regulation success

Some fMRI NFB studies demonstrated that a minority of participants are not able to learn self-regulation [74, 128, 129]. As mentioned earlier, regulation success was shown to be correlated with a certain timing of activation of frontal brain regions [115]. However, in terms of behavioural variables, this group of non-responders is very poorly characterised for fMRI neurofeedback. Therefore, future studies should look if and how education, personality traits and habits may influence regulation success.

1.4 Pain processing as a target for real-time fMRI

One possible target for real-time fMRI NFB is pain processing. By learning to regulate areas that are implicated in the sensation of pain, subjective pain strength could be decreased voluntarily in subjects with acute or chronic pain. To get an idea about the feasibility of pain fMRI NFB and possible target regions, I will take a closer look at the underlying mechanisms of pain in the following section.

1.4.1 Introduction to acute and chronic pain

Pain is an unpleasant sensory and emotional perception in response to potential or actual tissue damage. Under normal circumstances, pain is only present as long as the tissue damage or potential tissue-damaging stimulus is present (acute pain). However, under certain conditions, there can be a maladaptation due to repeated painful stimulation that leads to chronic pain, even in the absence of any tissue damage or painful stimulation.

About 20-30% of the general population experiences chronic pain [130–132]. In the USA the total annual costs of pain are estimated to be around 560 - 635 billion $ including health care and productivity loss costs [131]. Around 18 billion $ of this sum is made up by chronic pain medication alone [133]. Chronic pain is often accompanied by comorbidities including depression and sleep disturbances [132].

Pharmacological treatment of chronic pain relies on opioids and non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid [131]. However, opioids bear the risk of severe side effects including respiratory depression as well as tolerance following long-term use. In addition, there is a high risk of abuse and misuse of opioids. NSAIDs are less potent pain killers and can also lead to adverse events

such as renal failure and heart attack. Therefore, non-pharmacological treatment options should be explored. Psychological treatment includes self-regulatory [134], behavioural or cognitive-behavioural approaches [131, 135]. These options showed some positive effects [136] but are still rarely used. In conclusion, a huge amount of chronic pain patients might benefit from supplementary pain treatments.

1.4.2 Pathophysiology of pain

The molecular basis for acute pain detection are special nociceptive receptors in the cell membrane of certain peripheral nerve fibers called nociceptors. The receptors differ depending on the pain modality including heat, cold, mechanical and chemical pain. Heat pain receptors include the capsaicin-sensitive transient receptor potential (TRP) ion channel TRPV1 that has a thermal activation threshold of around 43°C [137–139] and a subpopulation of potassium channels [140]. For cold pain the most prominent receptor is TRPM8, which reacts to temperatures below 30°C and menthol [141]. For mechanosensory transduction of pain purginergic P2X receptors [142] as well as certain potassium channels are essential [140]. Furthermore, acid-sensing channels (ASICs) are part of the chemical pain sensing mechanism [143]. Moreover, a variety of channels, including voltage-gated sodium and calcium channels as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and serotonin receptors are important for nociceptor excitability and other processes such as inflammation and pain sensitisation [140].

The cell bodies of the nociceptors that express the aforementioned receptors lie in the dorsal root ganglia and the trigeminal ganglion [144, 145]. Dorsal root ganglion cells synapse onto interneurons in the dorsal horn of the spinal cord. There are different types of nociceptors that differ in conduction speed (i.e. myelinisation) and threshold. While the myelinated A delta fibers transduce acute, well-localised pain, C fibers mediate poorly-localised pain with a much slower speed [144]. Once the pain stimulus has been relayed to interneurons of the central nervous system it travels via spinothalamic and spinoreticulothalamic tracts to the thalamus and brainstem. From there information is relayed to multiple cortical structures including the somatosomatosensory cortex, the anterior cingulate cortex, the insula and prefrontal regions (see fMRI studies below for more details).

After acute tissue damage, pain usually subsides once the underlying damage has healed. However, in some patients the pain becomes chronic. While there are hints that persisting inflammation may impact the chemical environment of peripheral nerve

fibers [146], thereby leading to peripheral sensitisation, some of the most important changes leading to chronic pain take place within the central nervous system. Central sensitisation is mediated by a wide range of mechanisms. This includes the activation of quiescent NMDA receptor that will lead to a calcium influx increase, thereby strengthening synaptic connections in the long run [144,147]. Increased glutamatergic synapse strength will result in an augmentation of the pain response. In synergy to this mechanism, GABAergic and glycingeric interneurons are becoming less efficient or fewer [148, 149] so that there is a disinhibition of the projection neurons, also leading to sensitisation.

1.4.3 Magnetic resonance imaging of pain

Acute and chronic pain have been intensively studied using magnetic resonance imaging. Here, I will focus on literature looking at the brain. Nonetheless, there is also a growing number of studies investigating pain mechanisms in the spinal cord [150].

1.4.3.1 Structural brain changes

Structural changes induced by pain have been investigated by means of voxel-based morphometry (VBM) using anatomical scans. Understandably, short-term acute pain is not expected to induce significant structural changes. There are two studies that looked at the impacts of repeated exposure to acute pain on healthy subjects [151,152]. Teutsch et al. showed that repeated noxious stimulation over several days was accompanied by a grey matter volume increase in the premotor cortex, medial cingulate cortex, primary somatosensory cortex, inferior parietal lobule, and medial temporal gyrus [151]. The second study looked at the relationship of cortical thickness and heat and cold pain sensitivity. It was found that the cortical thickness of the primary somatosensory cortex is correlated with the individual heat and cold pain sensitivity. Additionally, medial cingulate and orbitofrontal cortex thickness correlated with heat pain sensitivity as well [152].

Concerning chronic pain, most studies show a grey matter reduction in the insula and anterior cingulate cortex [153–159]. Obviously, the effect size and localisation of affected areas may vary depending on the disorder (e.g. chronic headache may have different effects on the brain than chronic back pain or temporo-mandibular disorder). Other regions that demonstrate abnormal grey matter volume in chronic pain in general include the PFC, the medial cingulate cortex, the somatosensory cortex as well as sub-cortical regions such as the brainstem and the thalamus [153,154]. Interestingly,

the basal-ganglia often show an increased grey matter volume [160–162]. Some studies suggest that chronic pain causes these brain changes rather than the brain changes being the underlying cause of the pain. For example, one study suggests that thalamic grey matter volume correlates with the duration of pain [163]. In addition, several studies showed that the effect of pain on the brain can partially be reversed by resolving the cause of the pain in different disorders including primary hip osteoarthritis, chronic lower back pain and chronic post-traumatic headache [155, 159, 164, 165]. However, there are also some preexisting differences in pain-related brain areas correlated to personality traits [154, 166, 167]. Therefore, some people might be more vulnerable to chronic pain than others. In sum, chronic pain seems to specifically reduce grey matter volume in higher cognitive areas associated with pain interpretation and salience.

In addition to grey matter alterations, white matter changes have been investigated in chronic pain using diffusion tensor imaging (DTI). The first studies show an increase in connectivity between the PFC and insula [156] as well as between the PFC, thalamus and anterior cingulate cortex [168]. A decrease in white matter connectivity was detected between the PFC and basal ganglia as well as between the basal ganglia and thalamus [153, 156, 168]. Moreover, the corpus callosum showed altered connectivity with the frontal pole, PFC and cingulum [156, 169]. In addition, the fractional anisotropy of several pain-related areas including the insula and cingulum seems to correlate with pain characteristics such as pain severity and catastrophising [170]. The decrease in basal ganglia connectivity might hint at a decrease in the anti-nociceptive regulation of the basal ganglia [154] while other connections that are involved in pain interpretation may be strengthened.

1.4.3.2 Functional magnetic resonance imaging

FMRI has been extensively used to assess pain mechanisms using pain-relevant tasks in healthy subjects and chronic pain subjects. Recently, resting-state fMRI, which does not require participants to perform any specific task, has also gained popularity.

Resting-state functional connectivity changes

Resting-state functional connectivity looks at the temporal correlation of brain areas when the brain is at rest i.e. not involved in a specific task. Several networks

have been shown to be functionally connected during rest including the default mode network (DMN), which is deactivated during externally-oriented tasks [171, 172]. Apart from the DMN, several other networks that seem to correspond to certain functions can be identified with resting-state fMRI [173].

While several studies conclude that the DMN is deactivated during pain [174–176], recent work suggests that this deactivation might be due to pain anticipation [177]. Instead, during pain perception per se, the DMN may be active [177]. This might explain why a previous study found that the DMN deactivated to a lesser extend with stronger pain stimuli [178]. Therefore, future studies are needed to confirm whether the DMN indeed activates due to pain with confounding pain anticipation-driven deactivation. Concerning other networks, resting-state fMRI seems to activate attention networks including the insula and pain-sensitive areas such as part of the cingulate and somatosensory cortices [175, 177, 179].

Unsurprisingly, in chronic pain patients, the pain-processing network seems to be altered in comparison to healthy subjects [180]. Moreover, DMN deactivation during tasks seems to be decreased in chronic pain [181] supporting the idea that pain may increase DMN activation. In addition, connectivity between the DMN and pain-related regions seems to be impacted in chronic pain [182, 183].

Task fMRI in acute and chronic pain

Acute painful stimulation consistently activates the primary and secondary somatosensory cortex, the insula and the anterior cingulate cortex [184, 185]. The somatosensory cortex is involved in basic perception of touch including painful stimuli. While the posterior insula is most likely involved in the qualitative perception of pain-specific stimuli [186], anterior insula activation is less specific [187]. The anterior insula is implicated in interoceptive awareness and the saliency network, mediating increased alertness in response to external stimulation [188]. Another region involved in saliency and attentional networks is the anterior cingulate cortex [189–191]. In addition, the anterior cingulate cortex seems to play a role for pain affect, expectation and distraction [192, 193] as well as for emotional aspects of pain [194–197]. Therefore, both of these region seem to act as multisensory integration sites of different pain aspects. Apart from the anterior cingulate cortex and the anterior insula, the PFC and parietal association areas seem to be other higher-level cognitive areas that respond to pain [184]. These regions influence other pain-responsive areas such as

the amygdala, the thalamus and the basal ganglia [198].

Interestingly, different pain modalities seem to differ slightly in their activation patterns. While thermal pain produced a stronger activation in a number of regions including the insula, anterior cingulate cortex and PFC, mechanical pain resulted in a stronger activation of the supplementary motor area and supramarginal gyrus [199]. In addition, gender seems to influence pain processing [200, 201].

Studies looking at chronic pain patients often report that the normal pain response is altered [202–205]. However, three coordinate-based meta-analyses showed conflicting results. One meta-analysis came to the conclusion that chronic pain enhances activation of the secondary somatosensory cortex, contralateral supplementary motor area and ipsilateral cerebellum while activation likelihood was diminished in the primary somatosensory cortex, insula, anterior cingulate cortex, PFC and thalamus [199]. In contrast, another meta-analysis showed increased activation likelihood of the right anterior insula, left anterior cingulate cortex and left secondary somatosensory cortex and decreased activation likelihood of the left posterior insula and right supplementary motor cortex [206]. The most recent meta-analysis [207] hypothesized that discrepancy in the results was caused by methodological differences and that both analyses did not correct for cases in which the same subjects were involved in different experiments thus leading to non-independent studies. In this last meta-analysis, no significant differences in activation patterns in response to pain between chronic pain patients and healthy subjects were found. However, if pain stimulation was applied specifically at the body site that was most implicated in chronic pain, activation likelihood was significantly increased in the left putamen, the right mid to posterior insula and the left middle frontal gyrus. It was proposed that the putamen plays a key role in mediating maladaptive processes leading to chronic pain, as it is a coordinator of nociceptive, sensory and cognitive pain processing [207, 208].

Real-time fMRI neurofeedback studies

There have been several attempts to influence pain processing by means of real-time fMRI NFB. DeCharms et al. [56] were the first ones to demonstrate that fMRI NFB can be used to down-regulate the rostral anterior cingulate in healthy subjects and chronic pain patients. They showed that real feedback was superior to sham feedback and other biofeedback methods in terms of pain reduction for healthy subjects. Even for chronic pain patients, the anterior cingulate regulation was accompanied by a

decrease in pain levels. However, the group later stated that they were having troubles replicating their results [209]. A more recent study tried to compare the anterior cingulate and posterior insula as possible target regions for pain regulation [64]. The authors found that down-regulation of both regions was possible but up-regulation of the anterior cingulate was not successful. They did not find any significant differences in pain perception in the different conditions, which might in part be caused by the failure to up-regulate the anterior cingulate. Another group looked at patients with postherpetic neuralgia [78] and found that six out of eight patients in the experimental group were able to regulate the rostral anterior cingulate. This regulation success was not achieved by the sham group. They also found a significantly different change in subjective pain perception of the experimental group in comparison to the sham group.

1.4.4 Conclusions and suitability for neurofeedback

In conclusion, there are several pain-sensitive brain regions that could function as a real-time fMRI NFB target. Some pilot studies showed that fMRI NFB in the domain of pain is possible and can have favourable behavioural outcomes. However, the effect does not seem to be very strong and therefore it would be desirable to refine the method before conducting clinical trials to unequivocally prove the validity of fMRI NFB as a supplementary treatment for pain. Functional neuroimaging studies indicate that specifically the anterior insula and the anterior cingulate cortex seem to act as higher-level, multisensory integration sites of different pain components and are therefore likely to be good target areas for modulation.

1.5 Tinnitus as a target for real-time fMRI

Another domain that could employ real-time fMRI NFB as a supplementary treatment is tinnitus. In the following, I will describe the current view on the pathophysiological basis of tinnitus and advances in tinnitus imaging with MRI.

1.5.1 Introduction to tinnitus

Tinnitus is the perception of a sound often described as a ringing in the ear. This phantom percept is present in about 10-20% of the population [210–212]. The majority of people with tinnitus is not significantly impaired by their condition. However, a minority of about 1-3 % suffers severely [211]. In these cases, tinnitus often occurs

in combination with co-morbidities including depression or anxiety [213, 214]. In extreme cases, this can lead to suicide attempts due to tinnitus.

In the minority of the cases, tinnitus is objective, meaning that the sound has a physiological source. Usually this kind of tinnitus is caused by the perception of somatic sounds such as turbulent blood flow due to an aberrant internal carotid artery in the middle ear [215, 216]. In this case, the tinnitus is pulsatile rather than continuous. However, in most of the cases the sound perception exists continuously and without any underlying physical auditory stimulus, which is called subjective, continuous tinnitus. Here, I will primarily focus on subjective tinnitus as this is the target population for real-time fMRI NFB. Some tinnitus patients can influence their tinnitus by certain head or neck movements. For more information, please see case report in the appendix [217].

Currently, there is no gold standard for the treatment of tinnitus, although there are a few pharmaceutical and non-pharmaceutical options. Medications include intravenous lidocaine that induces a transient reduction of the tinnitus, but is not suitable for long-term use due to the intravenous administration that makes it impractical and prone to side-effects [218, 219]. In addition, anti-depressants have been used as tinnitus medication, especially for patients that also suffer from depression [220]. Among non-pharmaceutical options, tinnitus retraining therapy and normal cognitive behavioural therapy seem to be beneficial [221]. However, even these treatment options can only decrease the tinnitus effect. In order to develop causal therapies, the underlying pathophysiology needs to be determined.

1.5.2 Pathophysiology of subjective tinnitus in the central nervous system

Despite intensive research, there is still no consensus on the underlying cause of tinnitus. Tinnitus seems to arise as a response to auditory deprivation, due to damage of the auditory pathway, mostly at the level of the cochlear. The focal lack of auditory stimulation seems to activate homeostatic plasticity mechanisms. Therefore, the detection threshold is pathologically lowered, which leads to hyperactivity of the central auditory pathway in the absence of stimulation due to increased spontaneous firing rates [222]. This might even be the case when there is no hearing loss detected with normal audiometry [223]. In this case there might be a very focal damage of stereocilia in few hair cells leading to an increased spontaneous activity in a small

subset of auditory nerve fibers [224].

Additionally, tinnitus is often accompanied by hyperacusis, a condition in which patients have an increased sensitivity for tones, either globally or in a certain frequency range [225]. This may lead to normal tones being perceived as unpleasant or painful by these patients. Hyperacusis is correlated with an increased neural response to loud tones [226].

In animal studies, tinnitus is usually modelled by either sodium salicylate application or strong noise exposure. Except in the case of prolonged exposure to strong noise (120dB), the evoked tinnitus and hearing loss are usually transient in these studies.

Salicylate application was shown to be accompanied by a local modification of the spontaneous firing rate (SFR). An increase of the SFR has been reported for the auditory nerve [227], the external nucleus of the inferior colliculus (IC) [228, 229] and the secondary auditory cortex (AC) [230]. In contrast, a reduction of the SFR [231,232] or disparate responses of different types of neurons (high versus low initial SFR) [233] occurred in the primary AC. Similarly, in the anterior auditory field the SFR decreased [230]. However, salicylate injection significantly increased sound-evoked firing rates or local field potentials in the AC, most probably corresponding to hyperacusis [231, 232]. For a detailed review on the tinnitus inducing effect of salicylate, see Stolzberg et al. [234].

Non-traumatic noise exposure (4-20kHz tones, 68-80dB over 6 weeks) in cats was reported to locally increase the SFR for characteristic frequencies out of the stimulated range (lower than 5kHz and higher than 20Hz) as well as to enhance local neural synchrony (using multi-unit recordings) [235, 236].

Traumatic noise exposure (120-130dB, 1-4 h) causes transient (1h exposure) to chronic hearing loss at the stimulated frequencies and induces tinnitus. In the dorsal cochlear nucleus (DCN) this treatment leads to a long-term increase in SFR [237–240] and the degree of SFR increase correlates with the strength of behavioural evidence for tinnitus [241]. Similarly, in other parts of the auditory pathway traumatic noise exposure causes an initial decrease in the SFR followed by a long-term increase in SFR in the AC [242] and the IC [243]. Neural synchrony is increased from the beginning [242] and sound-evoked local field potentials are decreased in the IC but increased in the AC [244]. In a follow-up study using longer (2-4h) traumatic noise exposure to induce permanent damage, it was shown that this procedure induced a

reorganisation of the primary AC and that the increase in SFR was restricted to this reorganised area [235, 245].

In conclusion, animal research seems to show that tinnitus, especially if it is chronic, is associated to an increased SFR in parts of the central auditory pathway and increased neural synchrony. These findings are commonly explained by decreased inhibition due to an attempt to compensate for the missing input [246, 247], which also leads to increased excitability. Decrease of inhibition and increase of excitability have been shown to be present when auditory input is lost [248–250]. According to this theory, also called central gain theory, tinnitus and hyperacusis occur when neural amplification is used as a compensatory process in the central auditory pathway to compensate for the loss of input [251].

1.5.3 Magnetic resonance imaging of tinnitus

In order to see whether the previously presented findings from animal research can be translated to human tinnitus, non-invasive neuroimaging has been increasingly used over the recent years. I will present results from structural as well as functional magnetic resonance imaging in humans.

1.5.3.1 Structural brain changes

Earlier structural MRI studies using VBM found a grey matter decrease in auditory regions such as the thalamus [252] and the right IC [253] as well as in non-auditory regions including the nucleus accumbens with the surrounding subcallosal area [252] and the left hippocampus [253]. Another study [254], targeting Heschl's gyrus as a region of interest, found a reduction of grey matter volume within its medial part, even when controlling for age, sex, hearing loss, handedness and musical proficiency (non-musicians versus musicians). A study by Aldhafeeri et al. [255] showed a decrease of cortical thickness in the PFC, temporal lobe and limbic system. Unfortunately, this study did not control for moderate hearing loss (up to 60dB), so it remains unclear whether these alterations are linked to tinnitus or hearing loss.

More recent studies [256–258] did not confirm these changes, showing no significant grey matter differences between their tinnitus and control groups. The discrepancy in these results may be caused by a more careful control group matching for hearing loss in the later studies. Melcher et al. [257] showed that hearing loss at frequencies

above 8kHz was correlated with grey matter loss in some of the regions reported by the earlier studies. In a targeted region of interest analysis in one of the studies [258], a grey matter increase in the left primary AC was shown. This would be in agreement with the theory that increased neural activity underlies tinnitus.

Two other studies looked at the correlation of tinnitus characteristics and VBM changes. Schecklmann et al. [259] showed that grey matter volume in bilateral auditory areas including the insula and the primary AC is negatively correlated with tinnitus distress. However, this correlation did not survive multiple comparison correction when including additional regressors, including hearing loss, in the model. Vanneste et al. [260] found a positive correlation of tinnitus-related distress and tinnitus duration with cerebellar volume. However, as in the previously presented study, this correlation did not survive statistical testing when controlling for hearing loss. They also correlated the VBM measures with quantitative EEG and found no correlation, indicating that functional changes are not directly linked to structural changes, as assessed by VBM, in tinnitus.

In conclusion, no robust changes in grey matter volume can be attributed to tinnitus at the moment. Still, minor changes might be present, for example in the primary AC; this needs to be confirmed by further studies including region of interest analyses. There is also a need for close matching of the control group for hearing loss.

DTI was used to assess white matter alterations in tinnitus patients. The first such study [261] suggested a decrease of fractional anisotropy in some white matter tracts such as the left frontal arcuate fasciculus and the right parietal arcuate fasciculus for tinnitus subjects. Crippa et al. [262] found an increased white matter connectivity between the auditory cortex and the amygdala. In both studies, tinnitus subjects showed a mild to moderate hearing loss that was not present in the control group. Another study without hearing loss matching [263] showed decreased white matter connectivity of the left auditory-limbic circuit in tinnitus subjects.

A study [256] using a hearing loss-matched control group did not find any white matter differences due to tinnitus. Benson et al. [264] showed an increase in fractional anisotropy for the left anterior thalamic radiations, inferior and superior longitudinal fasciculi as well as the right inferior fronto-occipital fasciculus and superior longitudinal fasciculus. Another study [265] focused on auditory-limbic connections and compared a group of healthy controls with two tinnitus groups, one with and one without hearing loss. They found a decrease in the bilateral hippocampal fractional anisotropy

values for all tinnitus subjects. However, this effect was stronger for the group with hearing loss. In addition, they found correlations of hippocampal fractional anisotropy values and tinnitus measures such as tinnitus handicap inventory scores or visual analogue scales for tinnitus-induced attention deficit. Seydell-Greenwald et al. [266] found an increased connection of white matter tracts underneath the AC and IC, and showed that ventromedial PFC connectivity correlated positively with tinnitus loudness ratings in a region of interest analysis.

In sum, DTI research for tinnitus is biased by the accompanying hearing loss, which seems to induce decreased connectivity of the auditory pathway. Two of the DTI studies [262, 266] hinted at an increased anatomical connectivity of the auditory cortex in tinnitus patients. Future research is needed to validate these findings.

1.5.3.2 Functional magnetic resonance imaging

When looking at functional MRI there are task-based studies (see "Task fMRI") and resting-state studies (see "Resting-state functional connectivity changes") where subjects stay in the MRI scanner without performing any specific task. Both of these methods suffer from the noise that is present when acquiring MRI images, which impacts auditory stimulus presentation and the active networks throughout the acquisition. One attempt at resolving this problem is sparse acquisition [267, 268] that reduces scanner noise to certain sampling periods within the run. However, this technique reduces the number of acquired volumes, thus reducing statistical power. Additionally, it is not ideal for resting-state fMRI, as the noise becomes discontinuous, making it even more salient than continuous noise.

Resting-state functional connectivity changes

Considering resting-state functional connectivity, several studies described an increased auditory-limbic connectivity [269–272]. Kim et al. [271] found an increase in the connectivity between the bilateral AC and the amygdala. Another group found a similar trend, although in this case it did not survive statistical correction procedures [269, 272]. Maudoux et al. showed an increase of connectivity from the AC to the left parahippocampus, which was confirmed by Schmidt et al. [270]. Maudoux et al. also performed a graph connectivity analysis and found that while data from control subjects supported the separation into two anti-correlated networks, the tinnitus subjects only showed a presence of the first of these networks including the auditory cortex and the insula. In addition, Kim et al. [271] described increased functional

connectivity between regions involved in attention processes such as the dorsomedial PFC and AC. Another group found a decrease in connectivity between the AC and visual cortex [273], consistent with a decrease in overall connectivity in the visual cortex observed by Maudoux et al. [269]. Moreover, there seems to be decreased connectivity between the thalamus and a lot of brain regions including the PFC, auditory regions and the amygdala [274], hinting at disrupted thalamocortical functioning. A study looking at the correlation of brain connectivity and tinnitus characteristics found a link between connectivity values and several tinnitus features [275]. For example a positive correlation was found for tinnitus loudness and connectivity of the thalamus, hippocampus, and part of the caudate. Maudoux et al. [269] also found a correlation of mean connectivity of the posterior cingulate/precuneus and the tinnitus handicap inventory score.

It should be noted that only the Schmidt and Zhang et al. studies controlled for hearing-loss by including a control group with hearing-loss. In contrast to these results, another study did not find any functional connectivity differences [276]. The same has been reported in another study looking specifically at patients with non-bothersome tinnitus [277]. This might indicate that only bothersome tinnitus induces significant connectivity changes. To conclude, tinnitus seems to increase auditory-limbic connectivity as well as to impact the connectivity of attentional networks and decrease thalamo-cortical connectivity in patients with bothersome tinnitus.

Task fMRI

Here, I will summarise the findings of fMRI studies looking for brain activation differences in tinnitus patients in response to auditory stimulation. Two initial studies showed an asymmetric activation of the IC [278], thalamus and AC [279]. However, this was not confirmed in later studies [280–283] leading to speculations that the earlier results were caused by an interference with the background noise of the MRI and more unilateral hearing loss in the tinnitus subjects. In the later studies, elevated sound-evoked responses were found in the IC [280, 281]. However, another study reported that increased IC reactivity to sounds might be related to hyperacusis rather than tinnitus [282]. They found an increased sound-evoked response in the AC related to tinnitus. This was not confirmed by another fMRI study [283] also controlling for hyperacusis. Instead, an increased activation of the left medial geniculate body (thalamus) and right cochlear nucleus in the tinnitus patients, as well as a decrease in functional connectivity between the IC and the AC was found. In conclusion, tinnitus

may increase sound-evoked responses of the central auditory pathway in humans; however, the effects cannot be distinguished from hyperacusis unambiguously at the moment.

1.5.4 Conclusions and suitability for neurofeedback

In conclusion, animal research shows that tinnitus is accompanied by increased neural activity across the central auditory pathway, which is thought to be a homeostatic mechanism to compensate for the decrease in auditory input. With the help of fMRI, hyperactivity can also be detected in humans suffering from tinnitus, although it remains to be determined how much this effect is influenced by the presence of hyperacusis. Resting-state fMRI showed that in humans, tinnitus increases the link between the auditory cortex and the limbic system, which might also lead to an increased anatomical connectivity of the auditory cortex reflected by DTI. Tinnitus does not seem to cause robust grey matter changes. As the subcortical regions within the auditory network are rather small, functional neuroimaging of these structure is not trivial at the moment. Therefore, the auditory cortex, which was shown to be hyperactive in tinnitus (see pathophysiology and fMRI results above), seems to be the most promising target region at the moment.

Taken together, these findings indicate that future research should target the hyperactivity of the central auditory pathway as well as try to normalise the pathologic hyperconnectivity between limbic regions and the auditory cortex. A pilot study from our group [58] already showed that the majority of tinnitus patients are able to control auditory cortex activity via real-time fMRI NFB. In part of the subjects (2 out of 6) this resulted in a decrease of tinnitus symptoms. Therefore, future studies should explore NFB options for tinnitus patients further, aiming to increase behavioural impact and the number of participants.

1.6 Conclusion of state-of-the-art and research proposal

In conclusion, real-time fMRI NFB has shown very promising results in the last few years and may one day lead to improved treatment of disorders such as chronic pain or tinnitus. In order to make sure that fMRI NFB lives up to its promise, it is

important to optimise the neurofeedback setup to increase success rates.

During my PhD work I addressed four important questions:

- **Which brain processes take place during neurofeedback?**
  In an attempt to answer this questions I performed a meta-analysis using individual participant data. To this aim, we tried to contact authors of real-time fMRI NFB studies in healthy subjects to obtain original data. We then performed a group analysis over all subjects, thereby eliminating target-region specific effects that only occurred in subjects of a certain study. This process allows us to examine brain activity associated to neurofeedback.

- **How does the choice of target area influence neurofeedback success and processing?**
  This question has been addressed in a collaboration with Markus Breimhorst and colleagues looking at healthy subjects during pain processing. We compared between two pain-relevant target regions in order to see whether there are differences in brain activity and behavioural outcome (i.e. subjective pain ratings).

- **Do personality or habits impact neurofeedback success?**
  The same pain dataset was subsequently used to understand how pain coping habits influence brain and behaviour during neurofeedback.

- **How does feedback timing affect neurofeedback outcome?**
  Finally, a study was conducted to compare between the use of continuous and intermittent visual feedback in a clinical population. To this purpose, tinnitus patients underwent repeated real-time fMRI NFB.

Each of the four questions is discussed in one publication.

Publications

2.1 Publication 1

The aim of the first publication is to unravel the network of brain regions underlying self-regulation. Many studies looked at how specific regulation of a certain brain region is possible. However, it is unknown which brain regions are supporting and thus consistently active for self-regulation itself, independent of the target region. Therefore, we looked for data of published real-time fMRI NFB studies in healthy subjects. By selecting studies with very varying data acquisition parameters, paradigms and most importantly target regions, study-specific regulation effects would be canceled out over the multi-study analysis. The results of this meta-analysis will help to distinguish unspecific regulation effects from effects of target region regulation. In addition, it would be the first study to show the network underlying self-regulation per se. Publication 1 has been published in *Neuroimage* (volume 124, page 806-12) in 2016.

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Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated?

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ABSTRACT

An increasing number of studies using real-time fMRI neurofeedback have demonstrated that successful regulation of neural activity is possible in various brain regions. Since these studies focused on the regulated region(s), little is known about the target-independent mechanisms associated with neurofeedback-guided control of brain activation, i.e. the regulating network. While the specificity of the activation during self-regulation is an important factor, no study has effectively determined the network involved in self-regulation in general. In an effort to detect regions that are responsible for the act of brain regulation, we performed a post-hoc analysis of data involving different target regions based on studies from different research groups.

We included twelve suitable studies that examined nine different target regions amounting to a total of 175 subjects and 899 neurofeedback runs. Data analysis included a standard first- (single subject, extracting main paradigm) and second-level (single subject, all runs) general linear model (GLM) analysis of all participants taking into account the individual timing. Subsequently, at the third level, a random effects model GLM included all subjects of all studies, resulting in an overall mixed effects model. Since four of the twelve studies had a reduced field of view (FoV), we repeated the same analysis in a subsample of eight studies that had a well-overlapping FoV to obtain a more global picture of self-regulation.

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The GLM analysis revealed that the anterior insula as well as the basal ganglia, notably the striatum, were consistently active during the regulation of brain activation across the studies. The anterior insula has been implicated in interoceptive awareness of the body and cognitive control. Basal ganglia are involved in procedural learning, visuomotor integration and other higher cognitive processes including motivation. The larger FoV analysis yielded additional activations in the anterior cingulate cortex, the dorsolateral and ventrolateral prefrontal cortex, the temporo-parietal area and the visual association areas including the temporo-occipital junction.
In conclusion, we demonstrate that several key regions, such as the anterior insula and the basal ganglia, are consistently activated during self-regulation in real-time fMRI neurofeedback independent of the targeted region-of-interest. Our results imply that if the real-time fMRI neurofeedback studies target regions of this regulation network, such as the anterior insula, care should be given whether activation changes are related to successful regulation, or related to the regulation process per se. Furthermore, future research is needed to determine how activation within this regulation network is related to neurofeedback success.

Introduction

Neurofeedback using real-time functional magnetic resonance imaging (rt-fMRI) enables participants to obtain voluntary control over multiple brain regions. Studies using this technique have demonstrated that it may be possible to successfully manipulate brain areas including the anterior cingulate cortex (ACC, Weiskopf et al., 2003; Hamilton et al., 2011), the posterior cingulate cortex (Brewer and Garrison, 2014), the anterior insular cortex (AIC, Caria et al., 2007, 2010; Berman et al., 2013), posterior insular cortex (PIC, Rance et al., 2014), amygdala (Posse et al., 2003; Zotev et al., 2011; Bruhl et al., 2014), primary motor and somatosensory cortex cortices (Yoo and Jolesz, 2002; Berman et al., 2012), premotor area (Johnson et al., 2012), visual cortex (Shibata et al., 2011), auditory cortex (Yoo et al., 2006; Haller et al., 2013), substantia nigra/ventral tegmental area (Sulzer et al., 2013), nucleus accumbens (Greer et al., 2014) and inferior frontal gyrus (Rota et al., 2009; for a review see Ruiz et al., 2014).

Real-time fMRI neurofeedback has also been explored as a supplementary treatment for various neurological disorders. For instance, real-time fMRI neurofeedback has shown positive benefits for diseases such as schizophrenia (Ruiz et al., 2013), depression (Linden et al., 2012; Young et al., 2014), tinnitus (Haller et al., 2010), Parkinson's disease (Subramanian et al., 2011) and nicotine addiction (Canterberry et al., 2013; Hartwell et al., 2013; Li et al., 2013). However, effect size of neurofeedback varies and in a lot of studies some participants fail to attain self-regulation. The neural mechanisms of neurofeedback as used for self-regulation of bodily functions are not well understood, which may be a roadblock to achieving consistent outcomes between studies and successful translation into clinics.

One of the most important but least understood characteristics of neurofeedback is the specificity of activation during self-regulation. Previous investigations in real-time fMRI neurofeedback have attempted to control for specificity of the self-regulation using feedback from another region (deCharms et al., 2005), subtracting the mean activity of a reference slice that does not contain involved brain regions (Caria et al., 2007; Rota et al., 2009), or using post-hoc statistical methods (Blefari et al., 2015). In contrast, we are here interested in the regions that are additionally activated during self-regulation, that is, regions that are involved in the cognitively demanding task of neurofeedback regulation.

In their landmark study, deCharms et al. reported that reduced pain perception via ACC regulation may have resulted from the contribution of a higher order region despite rigorous controls (deCharms et al., 2005). If so, exactly which regions would be responsible for effects of self-regulation?

To answer this question, it is important to consider the cognitive processes involved during neurofeedback and the corresponding networks. One of these networks is the central executive network (CEN) that is active in most cognitively demanding task, likely reflecting working-memory involvement and decision-making (Koechlin & Summerfield, 2007, Miller & Cohen, 2001). It includes the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (Sridharan et al., 2008). In addition, the saliency network that is comprised of the AIC and the ACC as main components will be involved in neurofeedback relevant tasks including attentional control and monitoring. Menon and Uddin (2010) suggest that this network coordinates task-related information processing by recruiting various other, more specialized networks. For neurofeedback, these might include reward-learning areas, recruiting the striatum (Hollerman et al., 1998; Samejima et al., 2005; Daniel and Pollmann, 2014), the frontal cortex (Watanabe, 1996; O'Doherty et al., 2003) and areas responsible for interoception (Craig, 2002; Lerner et al., 2009) such as parts of the AIC. Neurofeedback will likely use subnetworks cutting through all the above-mentioned networks.

Indeed, studies using a single region of interest suggest involvement of the dorsolateral prefrontal cortex (dlPFC), the dorsomedial prefrontal cortex (dmPFC, Zotev et al., 2013), the ventromedial prefrontal cortex (vmPFC, Haller et al., 2010) and the anterior mid-cingulate cortex (Lee et al., 2012) to anterior cingulate cortex (Lawrence et al., 2013; Zotev et al., 2013) in the regulation process. A number of feedback studies show activation of the posterior ACC (pACC,), although this area was not targeted (e.g. Caria et al., 2007; Rota et al., 2009; Lee et al., 2012; Veit et al., 2012; Lawrence et al., 2013). Similarly, several studies reported activation of the insula during neurofeedback runs (e.g. Rota et al., 2009; Haller et al., 2010; Lee et al., 2012; Paret et al., 2014).

In the current investigation, we assess the brain network mediating regulation in real-time fMRI neurofeedback. We hypothesized that regardless of the target region used, a common brain network is involved in the regulation process itself. Consequently, we performed a meta-analysis using individual participant data (IPD meta-analysis) across multiple previously reported rt-fMRI neurofeedback studies with different target regions in order to cancel out target region-specific effects and identify those activations commonly related to the regulation process. It should be noted that, at the current stage, we cannot distinguish between self-regulation processes and other processes involved in neurofeedback including feedback processing and learning as the current study does not include control runs without feedback ("transfer runs"). Our results suggest the existence of a neurofeedback network consisting of the anterior insula, basal ganglia, dorsal parts of the parietal lobe extending to the temporo-parietal junction, ACC, dlPFC, ventrolateral prefrontal cortex (vlPFC) and visual association areas including the temporo-occipital junction.

Materials and methods

Study selection

Studies were selected based on a Web of Knowledge (https://apps.webofknowledge.com) search for the keywords: "real time fMRI", "real time functional" or "rtfMRI" (in January 2014) as well as studies indicated in the real-time community (rtfmri@sympa.ethz.cho, updated in August 2015 to rtFIN@utlists.utexas.edu) literature updates. This search provided us with a total of 316 publications. Next, we used the following selection criteria, 1) rt-fMRI neurofeedback, 2) 1.5 or 3.0 T

static field strength, 3) at least four healthy participants, and 4) at least three neurofeedback runs. These criteria were used to exclude technical proof-of-principle studies (usually with less subjects) as opposed to the "typical" neurofeedback studies using standard methodology. Twenty-eight studies were aggregated based on these criteria. Subsequently, we contacted the corresponding authors, and 12 of these corresponding authors agreed to provide us with the raw data of 12 studies that were used for the analysis.

Included studies

We were able to obtain 12 studies targeting nine different regions of interest, notably the insula (5), amygdala (2), primary motor cortex (1), premotor cortex (1), auditory cortex (1), visual cortex (1), anterior cingulate cortex (1), substantia nigra/ventral tegmental area (1) and the ventrolateral prefrontal cortex (1). Overall, a total of 175 subjects performed 899 neurofeedback runs. The studies are summarized in Table 1.

Analysis of MRI data

A standard mixed effects general linear model (GLM) analysis was conducted in FMRIB Software Library (FSL 5.0.6, FMRIB, Oxford, UK) (Smith et al., 2004). Preprocessing was performed using standard parameters (motion correction, co-registration, normalization to Montreal Neurological Institute (MNI) space, smoothing using a 5 mm Gaussian kernel).

The first level analysis used the individual study's block design as a regressor to model neurofeedback blocks. At the second level, all runs per subject were combined in a fixed effects analysis. Finally, a third level FMRIB's local analysis and mixed effects (FLAME1, Woolrich et al., 2004) analysis was conducted to combine all subjects of all studies resulting in an overall mixed effects analysis. At the third level, the analysis was performed including coding for the different studies as co-regressors.

Due to the restricted brain coverage of some studies, we performed this analysis two times. The first analysis used the entire data set and the restricted overlapping field of view (FoV) covered by all 175 subjects (see Supplementary Fig. 1 for FoV and regions of interest). In order to provide insight into regions outside of this small overlapping FoV, the analysis was repeated with a subsample of 8 studies and 103 subjects (first 8 rows of Table 1, see Supplementary Fig. 2 for FoV) with a larger overlapping FoV. All resulting activations were family wise error (FWE) multiple-comparison corrected using voxel-based thresholding at $p < 0.05$.

Results

The third level mixed effects analysis of all 12 studies yielded two main regions that are consistently activated during neurofeedback: the bilateral anterior insula and the basal ganglia. Considering the subsample analysis with a larger field of view ($n = 8$ studies) additional significant areas include the posterior ACC (pACC), the bilateral ventrolateral prefrontal cortex (vlPFC) and an area in the bilateral dorsolateral prefrontal cortex (dlPFC) extending to the premotor cortex (PMC), a large temporo-parietal area bilaterally, and lateral occipital areas including visual association areas and the temporo-occipital junction bilaterally (see Fig. 1). In addition, the analysis with 8 studies showed additional brain areas that are deactivated during neurofeedback, including the posterior cingulate cortex (PCC), the precuneus and bilateral transverse temporal area (see Fig. 1 and Table 2).

Discussion

The IPD meta-analysis of rt-fMRI neurofeedback studies with a variety of target regions identified a regulation network that includes notably the anterior insula, the basal ganglia, the temporo-parietal area, the ACC, the dlPFC, the vlPFC and the visual association area including the temporo-occipital junction (see Fig. 2).

Anterior insula activation is known to occur during interoceptive cognition and self-awareness processes (Craig, 2002; Critchley et al., 2004). Additionally, specifically the right AIC and the adjacent vlPFC are implicated in cognitive control tasks such as motor inhibition, reorienting and action updating (Levy and Wagner, 2011) using fronto-basal-ganglia connections. Similarly, basal ganglia are involved in interoceptive processes (Schneider et al., 2008) and also motivational processing (Lehericy and Gerardin, 2002; Arsalidou et al., 2013), as needed in feedback tasks. Moreover, the basal ganglia are essential for learning; whereas the dorsomedial striatum is known to be involved in declarative learning, the dorsoventral striatum is a key region mediating procedural learning (Yin and Knowlton, 2006; Balleine and O'Doherty, 2010). Interestingly, in their review Aron et al. pointed out that cognitive control tasks often employ a fronto-basal-ganglia network, which might explain our observation of both AIC/vlPFC and BG activation (Aron et al., 2014).

The temporo-parietal activation could be related to integration of the visual feedback and feedback related processes involving recall of memories (Zimmer, 2008) as well as self-processing and multisensory integration of body-related information (Arzy et al., 2006). PACC activation might reflect motivational aspects of the neurofeedback such as the rewarding effect of positive feedback and avoidance of negative

Table 1
Studies included in the current post-hoc analysis. In addition to the analysis across all studies, the analysis was repeated using the first eight studies (highlighted in bold) with a larger field of view.

Study	Target area	N	Sessions	Runs per session	Regulation	External stimuli	Blocks per run	Length of block [s]	Type of localizer
1) Berman et al. (2012)	**Primary Motor Cortex**	**10**	**1**	**3**	**UP**	–	**5**	**20**	**Functional**
2) Berman et al. (2013)	**Rostral Insula**	**13**	**1**	**4**	**UP**	–	**4**	**30**	**Functional**
3) Bruhl et al. (2014)	**Amygdala**	**6**	**4**	**2–3, total: 8–11 runs**	**DOWN, NO**	**Visual (pictures)**	**10**	**20**	**Functional**
4) Hui et al. (2014)	**Premotor Cortex**	**12**	**1**	**4**	**UP**	–	**7**	**30**	**Functional**
5) Johnston et al. (2011)	**VLPFC, IC, others**	**17**	**1**	**3**	**UP**	–	**12**	**20**	**Functional**
6) Paret et al. (2014)	**Amygdala**	**16**	**1**	**3**	**DOWN**	**Visual (pictures)**	**15**	**26**	**Functional**
7) Robineau et al. (2014)	**Visual Cortex (interhem. balance)**	**14**	**3**	**4**	**UP (one hemisphere stronger than other one)**	–	**3**	**30**	**Functional**
8) Sulzer et al. (2013)	**SN/VTA**	**15**	**1**	**3**	**UP**	–	**9**	**20**	**Anatomical**
9a) Emmert et al. (2014)-AIC	Anterior insula	14	1	4	DOWN	Pain	4	30	Functional
9b) Emmert et al. (2014)-ACC	ACC	14	1	4	DOWN	Pain	4	30	Functional
10) Frank et al. (2012)	anterior Insula	21	2	3	UP	–	7	30	Anatomical
11) Haller et al. (2013)	Auditory cortex	12	4	4	DOWN	Auditory	4	58	Functional
12) Veit et al. (2012)	Anterior Insula	11	1	3	UP, DOWN, NO	Visual (pictures)	6	9	Functional

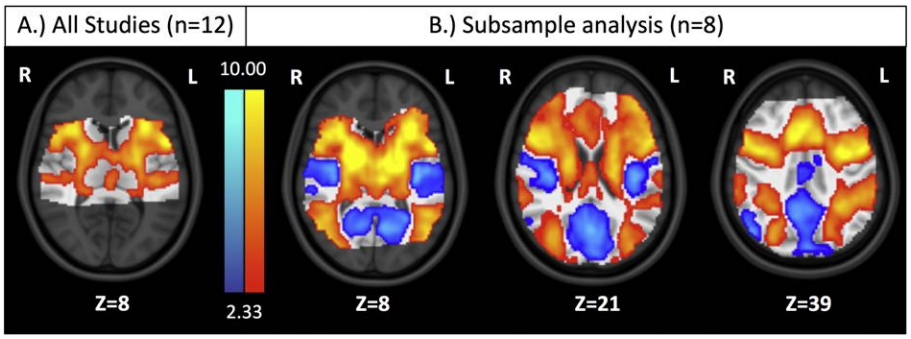

Fig. 1. Main effect of the third level mixed effects analysis. (A) Results from the main analysis using all 12 studies with a restricted field of view (FoV) (B) Results from the subsample analysis of eight studies with a larger FoV. The light gray area indicates the overlapping FoV, areas in red-yellow indicate regions that are active during regulation, while areas in dark–light blue depict areas with reduced activation during regulation.

feedback (Amiez et al., 2005; Magno et al., 2006; Posner et al., 2007). The dlPFC and premotor areas are implicated in the imagination of action, which likely relates to the mental imagery used during neurofeedback (Hanakawa et al., 2003; Lotze and Halsband, 2006). Finally, visual association area activation and the temporo-occipital junction activation may reflect visual imagery (D'Esposito et al., 1997; Zimmer, 2008) as well as processing of the visual feedback. To differentiate between effects of visual feedback and visual imagery one would have to include studies that use non-visual feedback. Unfortunately, to our knowledge, when conducting the search for real-time fMRI studies in 2014, there was only one study (Posse et al., 2003) using auditory feedback and this study did not fit our criteria (only two feedback runs for four of the six subjects).

In addition, our analysis showed some brain areas that were deactivated during neurofeedback, including the PCC as well as the precuneus. These areas are part of the default mode network (Raichle et al., 2001; Greicius et al., 2003; Raichle and Snyder, 2007), which is consistently deactivated during cognitively demanding tasks. Additionally, the transverse temporal area shows deactivations, possibly reflecting a shift of the focus away from scanner noise during the task i.e., a decrease of auditory activation due to visual feedback (Laurienti et al., 2002) and/or the task performance.

As most studies included in our IPD meta-analysis involved participants attempting to up-regulate a target brain area, the effect of regulation and the areas involved in the regulation process per se cannot be distinguished in these studies. One study aiming at down regulation of the auditory cortex (Haller et al., 2010) found that the dlPFC and vmPFC were simultaneously up-regulated, suggesting that these areas might be involved in the regulation process. In accordance with this study, we found an up regulation of the dlPFC. Additionally, we detected pACC activation that is close to the vmPFC area. Due to our restricted FoV we have no data available to validate the vmPFC activation itself. Increased basal ganglia and thalamus activation over runs has also been previously reported in a neurofeedback study (Lawrence et al., 2013). Other studies suggested that a part of the ACC and anterior mid-cingulate cortex is involved in brain regulation(Lee et al., 2012; Lawrence et

Table 2
MNI coordinates of the local maxima of all reported clusters of subsample analysis (n = 8) using a larger field of view.

Activations						
Cluster	Area	MNI coordinates			t-Stat value	z-Stat value
		X	Y	Z		
1	pACC	6	20	36	10.57	8.58
2	AIC R	32	26	4	12.30	9.49
	AIC L	−36	20	−2	13.66	10.14
3	vlPFC R	54	12	14	9.79	8.12
	vlPFC L	−50	8	4	11.00	8.81
	dlPFC/PMC R	42	0	42	10.05	8.27
	dlPFC/PMC L	−34	−4	40	11.42	9.04
4	Temporo-parietal R	62	−34	34	6.73	6.07
	Temporo-parietal L	−58	−32	32	7.64	6.73
	Parietal R	30	−48	40	5.42	5.05
	Parietal L	−30	−48	38	7.78	6.82
5	Occipital R	46	−58	12	7.62	6.71
	Occipital L	−46	−70	8	7.82	6.85
6	Basal ganglia (BG) & thalamus	Strong activation with several local maxima throughout BG (putamen, caudate nucleus, nucleus accumbens, globus pallidus) and thalamus.				
		20	0	10	11.04	8.83
		−20	0	12	11.07	8.85
Deactivations						
Cluster	Area	MNI coordinates				
		X	Y	Z		
1	Precuneus	0	−68	24	7.59	6.70
	PCC	8	−56	38	6.44	5.85
2	Temporal transverse L	−36	−20	16	9.72	8.08
	Temporal transverse R	38	−14	18	8.34	7.21
3	Parietal R	46	−68	36	6.71	6.06

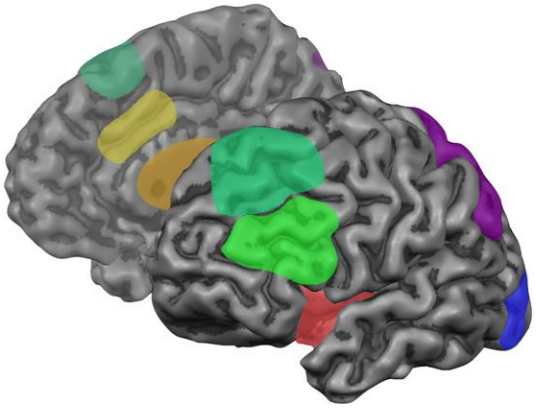

Fig. 2. Schematic display of main brain areas involved in self-regulation. This network includes the ACC (yellow), the dorsolateral PFC extending to PMC (dark green), the ventrolateral PFC (light green), the anterior insula (red), the basal ganglia and thalamus (orange), part of the inferior and superior parietal lobule extending to the temporo-parietal junction (violet) and the lateral occipital cortex extending to the temporo-occipital junction (blue).

al., 2013; Zotev et al., 2013). This result is also confirmed by our analysis. However, for the studies using a single ROI we cannot exclude the possibility that the shown effect was a result of the brain regulation (i.e., the activation was caused by the target region activation change) rather than the regulation process itself.

One study used several different visual regions of interest within the same subjects (Harmelech et al., 2015) and showed that some of the higher-level visual areas and the inferior parietal lobe (IPL) are easier to regulate than lower-level areas such as V1. Our study showed involvement of part of the IPL during self-regulation in general. This observation implies that the observed activation change in the IPL in this study might in fact be a mix between activation change due to successful neurofeedback and activation related to the cognitively demanding process of regulation per se. Note however, that this study employed auditory feedback, whereas all studies in our IPD meta-analysis used visual feedback. Unfortunately, this study does not report about common activation outside of their chosen target regions.

Other studies that assessed processes related to self-regulation including meditation, mental imagery and sham neurofeedback reported activations that are partly overlapping with our results. For example, an involvement of the lateral PFC and the insula was observed in experienced meditators during mindfulness meditation (Farb et al., 2007) underlining the importance of these areas for self-awareness in the present.

Additionally, some of the reported regions, especially the parietal and prefrontal areas, are implicated in mental imagery (McNorgan, 2012), which could be one cognitive component involved in neurofeedback regulation. Temporo-occipital activation can be observed specifically during visual imagery of form and motion (McNorgan, 2012).

Interestingly, another study assessing sham neurofeedback reported very similar activations (Ninaus et al., 2013). The authors reported the involvement of the bilateral insula, dorsomedial and lateral PFC, supplementary motor area, left ACC, right superior parietal lobe, right middle frontal activation, left supramarginal gyrus and left thalamus during attempted brain regulation with sham feedback in comparison to a passive viewing condition. This suggests that, independent of the outcome of the neurofeedback, a wide network of areas involved in cognitive control and sensory processing is recruited during attempted self-regulation. When looking at the comparison of viewing of moving bars and viewing of static bars, they found, among others, a strong activation in the middle occipital gyrus, very similar to the temporo-occipital activation found in this study, confirming that this activation is likely induced by the visual stimulation during feedback delivery. However, Ninaus et al. do not report a significant activation of the basal ganglia that showed strong activation in our IPD meta-analyses. This difference might either result from the difference in contrast (comparison against rest vs. comparison against passive viewing of moving bars) or might reflect a learning process specific to neurofeedback, that is not present in the sham feedback condition.

In order to test for neurofeedback-specific effects, some rt-fMRI studies include a transfer run without feedback presentation (e.g. Haller et al., 2013; Sulzer et al., 2013). These transfer runs can help to disentangle learning effects from the actual regulation process. In the future, when more studies using a transfer run will be available, a novel IPD meta-analysis could be run that includes a contrast of transfer runs in comparison to normal feedback runs to more specifically identify the neuronal mechanisms underlying visually-guided neurofeedback.

Our analysis combined up or down regulation studies under the assumption that the brain networks involved in the process of regulation per se should be active during regulation regardless of regulation direction. The only included study that used up and down regulation in the same subjects found IFG activation for up and down regulation, supporting this view that the regulation-related network is active regardless of the regulation direction (Veit et al., 2012). Note however that in this specific investigation, the IFG was also part of the target region and consequently there is a potentially confounding overlap between activations related to the process of regulation, and activations to be regulated within this region. Future, specifically designed studies that ideally directly compare up versus down regulation within the same participants are needed to further elucidate this issue.

Limitations

It might be interesting to further refine the data analysis by taking into account regulation success. It should be noted that there currently is no gold standard for the measurement of regulation success in healthy subjects. This could be either a neuroimaging variable (e.g. decrease of beta value) or a behavioral measurement (performance in a task relevant for the targeted area). In the absence of clearly established measurement for regulation success, notably in the current analysis across several experimental setups and target regions, it is not possible to unambiguously define a universal regulation success parameter across studies. When such a gold standard is established in the field, further investigation into correlations of activation with regulation success would be desirable to assess in detail regions related to successful neurofeedback regulation.

Further limitations include the limited FoV due to the individual slice positioning that was intended to include the individual region of interest and not necessarily whole brain coverage. We included only studies with visual feedback. Therefore, our results also reflect visual processing of the feedback. In all rt-fMRI studies, including those used for our analysis, learning processes could confound the regulation process as the subjects learn to self-regulate by watching the feedback.

The presented findings may be somewhat limited by the relatively low number of studies included (8 for large FoV, 12 for small FoV). The reason for this limitation is the rather small number of suitable studies available in this field and the fact that this IPD meta-analysis looked at the data itself requiring permission to use the original data. On the other hand the procedure of unifying the analysis steps using original data instead of comparing activation clusters reported in the literature should enhance the transparency and thus interpretability of results.

In addition, this analysis is retrospective and the design of the studies was not optimized for the IPD meta-analysis. Therefore, data acquisition parameters and paradigm (blocks, runs, sessions, up or down regulation, stimuli, instructions) vary considerably across studies. On the other hand, this can also be considered as strength as it indicates the general validity of our results as the data covers a range of different experimental setups and designs.

Outlook

This IDP meta-analysis is a first step towards an understanding of the underlying mechanisms of self-regulation. As this was a post-hoc analysis using studies that were designed independently, not all interesting scientific questions could be answered using these data. Here we mention a number of points that could be answered in future studies specifically designed for this purpose:

- What regions are implicated in the neurofeedback modality? E.g., study comparing visual and auditory feedback.
- Are there differences in the regulation matrix depending on the direction of regulation? E.g., study using up and down regulation within the same subjects for at least two different target regions.
- Which behavioral measures reflect neurofeedback efficacy independent of the target regions? Use these instead of/ in addition to target-region specific behavioral measures such as auditory, emotional or visual variables for regions such as auditory cortex, amygdala and visual cortex, respectively.
- What is the time line of neurofeedback learning (steady-state, linear or non-linear learning curve)?

Conclusion

Brain self-regulation during rt-fMRI neurofeedback involves a complex regulation network, including notably AIC, BG and the ACC. Taking into account the limitation that the current investigation is a retrospective IPD meta-analysis of rt-fMRI studies, which were not specifically designed for this purpose, our results suggest that some target regions of rt-fMRI neurofeedback studies (notably insula and ACC) are also implicated in the process of regulation per se. This may therefore represent a potential confound for the regulation of these areas.

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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.neuroimage.2015.09.042.

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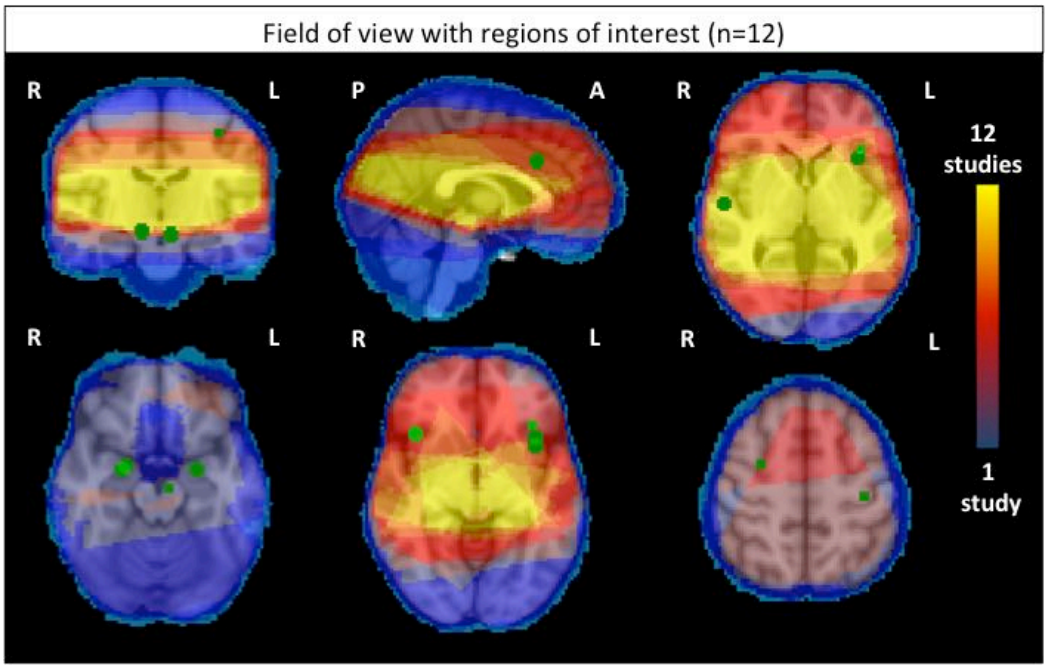
Supplementary Material Publication 1

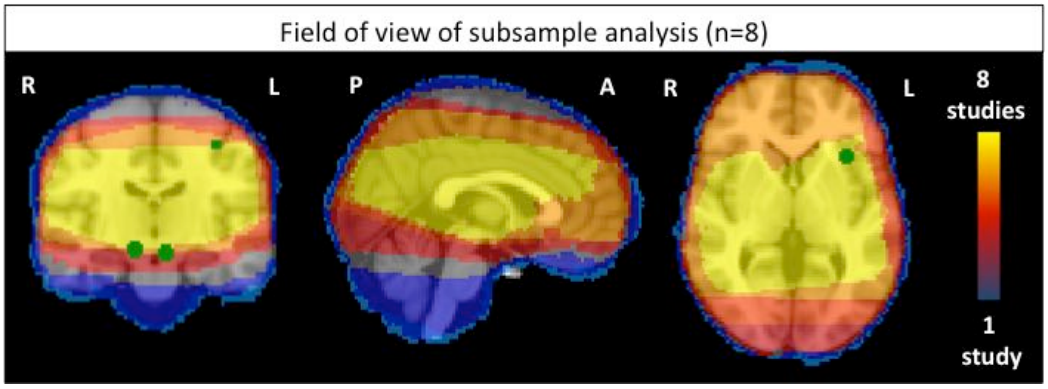
Supplementary Material

Supplementary Figure 1:



Overlap of field of view for all studies. The regions of interest are indicated in green. MNI coordinates: upper row: 2 -18 2; lower row: Z=18, Z=-6, Z=54.

Supplementary Figure 2:



Overlap of field of view for all studies included in the subsample analysis. MNI coordinates: 2 -18 2.

2.2 Publication 2

The second publication looked at the target region selection, comparing between two suitable pain NFB target areas, namely the anterior cingulate cortex and the anterior insula, in healthy subjects. This comparison could not only help to see which area might be best suited for real-time NFB pain studies in healthy participants and chronic pain patients in the future, but also give an insight into how the two target areas work within brain networks. Is one target area affecting other brain areas in a different way than the other when regulated, although both are part of a pain-responsive brain network?

This publication was a collaboration with a group from Mainz (Germany) that were responsible for the experimental setup and data acquisition. Please note that this publication was chronologically the first publication. It has been published in *Frontiers in behavioral neuroscience* (volume 8, article 350, 2014) as part of the research topic "Learned Brain Self-Regulation for Emotional Processing and Attentional Modulation: From Theory to Clinical Applications".

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Comparison of anterior cingulate vs. insular cortex as targets for real-time fMRI regulation during pain stimulation

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Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback allows learning voluntary control over specific brain areas by means of operant conditioning and has been shown to decrease pain perception. To further increase the effect of rt-fMRI neurofeedback on pain, we directly compared two different target regions of the pain network, notably the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC). Participants for this prospective study were randomly assigned to two age-matched groups of 14 participants each (7 females per group) for AIC and ACC feedback. First, a functional localizer using block-design heat pain stimulation was performed to define the pain-sensitive target region within the AIC or ACC. Second, subjects were asked to down-regulate the BOLD activation in four neurofeedback runs during identical pain stimulation. Data analysis included task-related and functional connectivity analysis. At the behavioral level, pain ratings significantly decreased during feedback vs. localizer runs, but there was no difference between AIC and ACC groups. Concerning neuroimaging, ACC and AIC showed consistent involvement of the caudate nucleus for subjects that learned down-regulation (17/28) in both task-related and functional connectivity analysis. The functional connectivity toward the caudate nucleus is stronger for the ACC while the AIC is more heavily connected to the ventrolateral prefrontal cortex. Consequently, the ACC and AIC are suitable targets for real-time fMRI neurofeedback during pain perception as they both affect the caudate nucleus, although functional connectivity indicates that the direct connection seems to be stronger with the ACC. Additionally, the caudate, an important area involved in pain perception and suppression, could be a good rt-fMRI target itself. Future studies are needed to identify parameters characterizing successful regulators and to assess the effect of repeated rt-fMRI neurofeedback on pain perception.

Keywords: real-time fMRI neurofeedback, realtime fMRI, pain, anterior cingulate cortex (ACC), anterior insular cortex, insular cortex

INTRODUCTION

Pain perception has a great impact on individual emotional health as pain is associated with anxiety (Asmundson and Katz, 2009), anger (Trost et al., 2012), fear (Leeuw et al., 2007a,b; Vlaeyen and Linton, 2012), and worry (Eccleston and Crombez, 2007; Linton, 2013). Thus, not surprisingly, chronic pain increases the risk of depression and suicide (Turk et al., 1995; Geisser et al., 2000; Bair et al., 2003; Ilgen et al., 2008; Denkinger et al., 2014). Pharmacological intervention remains the mainstay of chronic pain treatment. As most chronic pain patients are treated with a combination of pain medications and over long periods of time (Muller-Schwefe et al., 2011), cumulative drug-related side effects pose a considerable risk of adverse effects for these patients (Jouini et al., 2014), highlighting the importance of alternative and supplementary pain therapies.

One novel technique that shows potential in the treatment of chronic pain is real-time functional magnetic resonance imaging (rt-fMRI), which allows volitionally influencing activation of a targeted brain area by means of operant conditioning when being supplied with a corresponding feedback signal. This technique could be employed to reduce brain activation in pain network target areas with the aim to decrease the subjective pain perception.

Abbreviations: ACC, anterior cingulate cortex; AIC, anterior insular cortex; aMCC, anterior mid-cingulate cortex; ANOVA, analysis of variance; BOLD, blood oxygenation level dependent; fMRI, functional magnetic resonance imaging; GLM, general linear model; ICA, independent component analysis; MELODIC, multivariate exploratory linear optimized decomposition into independent components; MPRAGE, magnetization prepared rapid gradient echo; NRS, numeric rating scale; PIC, posterior insular cortex; PFC, prefrontal cortex; ROI, region of interest; rt-fMRI, real-time fMRI; SEM, standard error of the mean.

A pilot study showed that it is possible to regulate the anterior cingulate cortex (ACC) as a target brain region using rt-fMRI for chronic pain patients as well as healthy participants during pain perception (Decharms et al., 2005). However, according to subsequent reports of the same group, these findings could not be replicated (Decharms, 2012). In line with this observation, rt-fMRI is generally still in its early days, facing some limitations and confounds. High inter-individual differences in regulation success and small effect sizes make it difficult to assess the therapeutic use of this method. In an attempt to optimize the choice of the target region, which is a key factor of the rt-fMRI experiment, this study compares two possible target brain regions for feedback involved in pain processing in healthy subjects. The effect of the feedback on these target regions and other brain regions within the pain-responsive network will be assessed.

Acute pain perception starts with an external stimulus that activates peripheral receptors such as the vanilloid receptor (TRPV1), which is sensitive to temperatures above 43°C (Cesare and McNaughton, 1996) eliciting a depolarization of peripheral sensory neurons synapsing onto second-order dorsal horn neurons (Basbaum and Jessell, 2000) in the spinal cord. These fibers ascend to the thalamus relaying information to the somatosensory cortex, the ACC and the insular cortex (IC). Additional projection neurons from the dorsal horn to the parabrachial nucleus in the brainstem engage the ACC and the IC via the amygdala. Apart from this ascending connection, cortical pain areas such as the primary and secondary somatosensory cortex as well as the posterior insula (PIC), which are implicated in basic pain perception, are heavily interconnected (Apkarian et al., 2005). The same is true for higher-level areas involved in pain processing, including the ACC, the anterior insula (AIC) and prefrontal cortical areas exerting top-down regulation on the thalamus and the amygdala in turn. In addition, the basal ganglia are activated through multiple pathways including the thalamus, the amygdala and cortical areas (Borsook et al., 2010). While areas that are involved in basic sensory pain processing, such as the PIC, are predominantly activated contralateral to the pain stimulus, higher-level processing areas implicated in pain interpretation including the AIC are activated in a bilateral fashion (Brooks et al., 2002).

Ongoing nociceptive input from injuries leads to a hyperexcitability of the nervous system, in a process that resembles long-term potentiation called central sensitization (Drdla and Sandkuhler, 2008; Woolf, 2011), in addition to a decrease of tonic inhibition (Moore et al., 2002; Keller et al., 2007). This hyperalgesia has the purpose of facilitating the healing processes of the injured tissue. However, central sensitization can persist after tissue healing leading to chronic hyperalgesia and even pain perception in the absence of painful stimuli (Voscopoulos and Lema, 2010; Woolf, 2011). Furthermore, pathological changes in the descending modulatory pathways might also contribute to the emergence of chronic pain (Porreca et al., 2002; Ossipov et al., 2010).

Functional brain imaging showed abnormal activation in the rostral ACC and the frontal cortex in certain chronic pain populations (Baliki et al., 2006; Berman et al., 2008; Jensen et al., 2009; Burgmer et al., 2010). Additionally, chronic pain patients show altered functional connectivity of the prefrontal cortex (PFC) and the insula with the default mode network (Napadow et al., 2010; Baliki et al., 2011). Similarly, structural imaging revealed gray matter reductions within the PFC, the ACC and the IC (Bushnell et al., 2013). On a molecular level, chronic pain patients seem to show altered endogenous release for the glutamatergic and GABAergic system as well as a decrease in receptor binding of the opioidergic system in these areas (Bushnell et al., 2013). These anatomical and molecular changes might not only alter pain regulation, but also affect decision making (Grace et al., 1999; Leavitt and Katz, 2006; Munguia-Izquierdo and Legaz-Arrese, 2007).

Some studies also suggest that these changes can be partly reversed, for example, in cases where there is an underlying painful condition that can be removed after years (Gwilym et al., 2010; Seminowicz et al., 2011). Moreover, the pain modulation system consisting of the PFC, ACC, and AIC was shown to be modulated by cognitive measures such as meditation or cognitive behavior therapy (Grant et al., 2011; Gard et al., 2012; Jensen et al., 2012). Thus, it seems useful and feasible to regulate these areas using rt-fMRI neurofeedback. Before looking into possible neurofeedback effects for chronic pain patients, we aim to optimize target ROI selection for pain neurofeedback in healthy subjects during pain stimulation as a first step. Future studies are needed to make sure that these target ROIs can be regulated in chronic pain patients as well.

The ACC and the AIC seem to be particularly important in perceiving pain intensity (Favilla et al., 2014). Therefore, these two regions of the medial pain system (Treede et al., 1999) were considered the most promising rt-fMRI target regions for cortical pain processing. The ACC was also the subject of a recent rt-fMRI neurofeedback study testing feasibility of pain regulation for the rostral ACC and PIC (Rance et al., 2014). They postulated that sensory pain aspects might be more related to PIC activation while affective aspects are more related to ACC activation. In this context, it is interesting to investigate how the AIC—implicated in another aspect of pain, namely cognitive control processes—can be regulated.

The ACC has been associated to several functions relevant to pain processing including saliency (Seeley et al., 2007; Iannetti and Mouraux, 2010), attention (Bush et al., 2000; Weissman et al., 2005), and emotion (Bush et al., 2000; Shackman et al., 2011). It is furthermore linked to affective processing of painful stimuli (Vogt et al., 1996; Rainville et al., 1997). Studies already showed that it is possible to target the ACC in smokers (Canterberry et al., 2013; Hartwell et al., 2013; Li et al., 2013) and chronic pain patients as well as healthy participants during pain perception (Decharms et al., 2005). In the latter study, regulation of the ACC activation using rt-fMRI neurofeedback even resulted in a decrease of pain intensity ratings. Other behavioral interventions that have been shown to modulate ACC activation include hypnosis (Rainville et al., 1997; Faymonville et al., 2000), modulation of pain expectation (Sawamoto et al., 2000; Bingel et al., 2011), and distraction (Bantick et al., 2002; Valet et al., 2004).

The IC can be divided into the anterior and the PIC that serve distinct functions in pain processing. The PIC seems to be involved in basic pain and touch sensation (Greenspan and Winfield, 1992), receiving direct spinothalamic input

(Garcia-Larrea, 2012). Lesions in this area lead to pain and temperature deficits (Greenspan et al., 1999; Birklein et al., 2005). In contrast, AIC lesions usually do not seem to have a direct impact on pain perception *per se* (Greenspan et al., 1999). The AIC is implicated in a wide variety of functions, including visceral sensation and an integrative role in perception-action coupling possibly by mediating heightened alertness to prepare for action (Sterzer and Kleinschmidt, 2010). It seems to be engaged in affective-motivational processes of pain perception as a disconnection of the AIC from the PIC leads to a decrease of emotional pain reaction while nociceptive recognition remains intact (Berthier et al., 1988). Up-regulation of the AIC was shown to be possible (Caria et al., 2007; Veit et al., 2012) using recall of personal and affectively relevant events or focused attention on arising bodily sensations (Lawrence et al., 2013). It was shown that it is even possible to target subjects with clinical disorders such as schizophrenia (Ruiz et al., 2013) or depression (Linden et al., 2012). While these studies suggest that AIC regulation can be used to increase certain affective states and control, there is no specific data looking at the influence of the AIC down-regulation on pain perception.

In this work, we directly compared two possible target regions for rt-fMRI neurofeedback in pain, notably the AIC and the ACC, in order to determine the most efficient target region for future neurofeedback studies in pain processing.

MATERIALS AND METHODS

PARTICIPANTS

The local ethics committee in Mainz approved the study that adhered to the Declaration of Helsinki. Twenty-eight healthy subjects (mean age: 27.5 ± 2.3 years, 14 male, 14 female) gave written informed consent prior to participation. Participants were randomly split into two groups of $N = 14$ each, including seven male and seven female participants per group (group 1: 27.6 years ± 2.1, group 2: 27.4 ± 2.6 years). The first group received feedback from the left anterior insula (lAIC) as a target region, while the second group did so from the ACC. Exclusion criteria were defined by acute or chronic pain, pregnancy, severe neurological or internal disorders, intake of painkillers and contraindications for MR-measurements. Participants were paid for participation in the study.

REAL-TIME EXPERIMENT

The experiment consisted of two stages. First, a functional localizer run with an ON-OFF block design of eight blocks alternating between continuous painful stimulation for 30 s and rest for 30 s each was performed to identify the individual target regions. The target region was chosen based on significant activation within the lAIC/ACC during the functional localizer. Thereafter, four identical neurofeedback runs were performed consisting of a block design of four rest and regulation blocks (30 s each) preceded by 15 s of initial rest before the first block. Online data analysis was performed using TurboBrainVoyager version 2.8 (Brain Innovation, Maastricht, The Netherlands).

The target region was chosen based on significant activation within the lAIC/ACC during the functional localizer (summarized in Supplementary Table 1). Regulation blocks included the same pain stimulation as during the localizer. During this period of the neurofeedback runs, subjects were asked to decrease the blood oxygen level dependent (BOLD) activation level in the target region, which was visualized to them by a yellow line. The background color of the yellow line indicated to either keep the yellow line constant (black = rest blocks, no heat pain) or to decrease the amplitude of the yellow line (blue = down-regulation, heat pain). Subjects could freely choose their mental strategy to reach this objective.

PAIN STIMULATION AND RATING

An MR compatible thermode (TSA 2001, Medoc Ltd, Ramat Yishai, Israel), placed at middle of the lower right volar forearm, was used for pain stimulation. This 30 × 30 mm Peltier device has a default temperature of 32°C. Before the start of the experiment the thermode temperature was adjusted for each participant to elicit a subjective pain intensity of 7 out of 10 on the numeric rating scale (NRS). The thermode temperature for pain stimulation remained constant throughout the experiment [Ramp rate: 4°C/s, mean ramp and fall time for AIC-group: 3.83 s (*SD* 0.26) and for ACC-group: 3.64 s (*SD* 0.32), mean plateau for AIC-Group: 22.35 s (*SD* 0.53) and for ACC-Group: 22.71 s (*SD* 0.64), mean temperature for AIC-Group: 47.08°C (*SD* 1.1) and for ACC-group: 46.42°C (*SD* 1.4)]. After each run pain ratings were obtained using a 11-point NRS ranging from 0 (not painful) to 10 (most painful).

fMRI DATA ACQUISITION

Imaging was performed on a 3T MRI Scanner (Siemens Tim Trio, Erlangen, Germany) using a 32-channel head-coil. For functional data acquisition an echo-planar imaging sequence (EPI, $TR = 1500$ ms, $TE = 30$ ms, matrix size 64 × 64, 24 slices, slice thickness 3 mm without gap) was utilized. Additionally, a high-resolution T1-weighted anatomical scan [magnetization prepared rapid gradient echo (MPRAGE), 1 mm isotropic] was acquired for later co-registration with the lower resolution EPI images.

STATISTICAL ANALYSIS BETWEEN RUNS AND GROUPS

Statistical testing for differences between runs and groups [pain ratings, region of interest (ROI) activation, s-modes] was performed in MATLAB 2012b (The MathWorks, Inc., Natick, USA). First, parameters were tested for normality using D'Agostino K-squared test. As normality was rejected for all our parameters of interest (pain ratings, ROI beta values, s-mode values), we used the non-parametric Friedman test (comparison between all runs) and *post-hoc* Wilcoxon tests (comparison between groups, and comparison of two runs when the Friedman test showed significant results). Bonferroni correction was applied to correct for multiple comparisons in the s-mode analysis (i.e., the number of independent components).

POST-HOC GLM ACTIVATION ANALYSIS OF THE FUNCTIONAL LOCALIZER

Off-line analysis was performed with SPM 8 (UCL, London, UK) and FSL 5.0 (FMRIB Analysis Group, University of Oxford, UK). Functional data was spatially realigned, co-registered to the anatomical data, normalized and smoothed (8 mm kernel) before

group analysis on the basis of a general linear model (GLM) using the block design described under Section Real-Time Experiment. For the fMRI analysis, family-wise error (FWE) corrected values of $p < 0.05$ are considered significant.

POST-HOC ROI ACTIVATION ANALYSIS OF THE NEUROFEEDBACK RUNS

GLM analysis for all four neurofeedback runs was performed analogous to the localizer run. As self-regulation was expected to increase with practice, we compared the first neurofeedback run with the subsequent runs in a ROI analysis for regions that were activated during the localizer run and known to be involved in pain processing, namely ACC, AIC, PIC. Based on our functional connectivity and ICA results in combination with its know implication in pain processing (Borsook et al., 2010), we included the caudate nucleus as an additional (a posteriori) ROI. Then, ROIs were defined as spheres with 1-cm diameter centered at the activation peaks within the relevant clusters from the group analysis of the functional localizer. This approach seemed more suitable than defining the ROIs on an individual level, as done for target ROI analysis, as not all subjects showed significant activation in all of the ROIs in the localizer run. Since regulation using rt-fMRI neurofeedback fails in some subjects, we restricted extensive *post-hoc* ROI analysis to those subjects who showed a decrease in activation in the target ROI; i.e., 9/14 for the AIC group and 8/14 subjects for the ACC group.

POST-HOC fMRI CONNECTIVITY ANALYSIS OF THE NEUROFEEDBACK RUNS

Using FSL 5.0, functional connectivity was assessed with a seed-based approach testing for correlation with the seed's time course orthogonalized to the global signal and the GLM regressor of main effect. Seed regions were both rt-fMRI targets, ACC and lAIC, respectively. The resulting connectivity maps of each subject were fed into a 2nd level GLM analysis to obtain group results.

In addition, an independent component analysis (ICA) was carried out in FSL using multi-session multivariate exploratory linear optimized decomposition into independent components (MELODIC) tensor ICA. So-called s-modes (i.e., measures of activation strength for every component in each subject) were compared between groups.

RESULTS

EFFECT OF NEUROFEEDBACK ON PAIN RATINGS

Pain ratings were lower in the neurofeedback runs compared to the localizer run [non-parametric, p(AIC group) < 0.001; p(ACC) < 0.01] in both groups, but did not show any significant differences between neurofeedback runs (see **Figure 1**, **Table 1**). Pain ratings did not differ between regulators and non-regulators ($p > 0.1$).

Neither pain ratings of the regulators nor the non-regulators changed significantly between neurofeedback runs.

FUNCTIONAL LOCALIZER

As expected, the functional localizer revealed significant activation within the insula, PFC and the ACC, all regions involved in pain processing (see **Figure 2**). Activation of the target region in each subject enabled the individual region of interest placement (see Supplementary Figure 1).

NEUROFEEDBACK RUNS

Seed-based connectivity of the left AIC and the ACC

Seed-based analysis at the group level showed the functional connectivity of the ACC and the AIC to other regions of the pain network (see **Figure 3A**). The analysis confirmed that ACC and

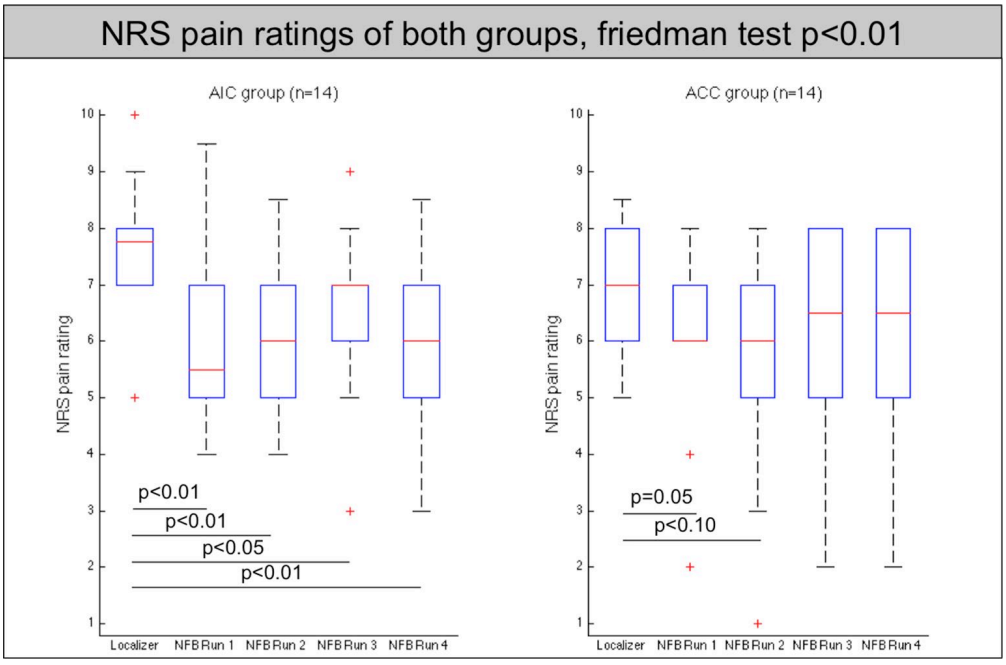

FIGURE 1 | Pain ratings of all participants (AIC-left, ACC-right) across localizer run and all neurofeedback runs. The red line indicates the mean value, the box indicates 25%/75% confidence intervals and the whiskers indicate the most extreme points within 1.5 times of the box length.

the AIC are strongly interconnected as well as showing connections to prefrontal areas. Interestingly, the ACC has high functional connectivity with the caudate nucleus that did not show up in the AIC connectivity map while the AIC group has an increased connectivity with the ventrolateral PFC (see **Figure 3B**).

Table 1 | Pain ratings on the numeric rating scale for all subjects.

Target ROI	Subject	Pain rating (0–10)				
		Localizer run	Run 1	Run 2	Run 3	Run 4
AIC	1	8.0	4.0	4.0	6.0	5.0
	2	7.0	5.0	6.0	6.0	6.0
	3	8.0	6.0	5.0	7.0	7.0
	4	7.0	5.0	6.0	6.0	4.0
	5	5.0	5.0	7.0	7.0	7.0
	6	9.0	7.0	6.0	7.0	4.0
	7	8.0	8.0	8.0	7.0	7.0
	8	7.0	5.0	5.0	7.0	6.0
	9	7.0	6.0	6.0	5.0	5.0
	10	7.5	7.0	6.0	7.0	6.0
	11	10.0	9.5	7.5	7.5	7.5
	12	9.0	7.5	8.5	9.0	8.5
	13	8.0	5.0	6.0	8.0	8.0
	14	7.0	5.0	4.0	3.0	3.0
ACC	15	6.0	6.0	7.0	8.0	8.0
	16	7.0	6.0	6.0	4.0	6.0
	17	8.0	8.0	8.0	8.0	8.0
	18	6.0	6.0	6.0	6.0	5.0
	19	8.0	7.0	7.0	8.0	8.0
	20	7.0	6.0	6.0	8.0	7.0
	21	8.5	6.0	6.0	6.0	6.0
	22	7.0	6.0	5.0	6.0	5.0
	23	7.0	6.0	5.0	5.0	6.0
	24	5.0	4.0	3.0	4.0	4.0
	25	8.0	7.0	7.0	7.0	7.0
	26	8.0	8.0	8.0	8.0	8.0
	27	8.0	6.0	7.0	8.0	7.0
	28	5.0	2.0	1.0	2.0	2.0

Effect of training (runs over time)

To assess a possible improvement in self-regulation over time, we looked for a decrease in activation in the later runs compared to the first run. To that aim, we first analyzed the activation within each individual target ROI (see **Table 2** and **Figure 4**). Data from subjects that showed a successful down-regulation (i.e., decrease of target region's activation level from the first to the average of the following runs) were used for a more extensive ROI analysis including the main brain areas involved in pain regulation (see **Table 3**).

The analysis of these regions showed that the decrease of the left AIC in the AIC group is accompanied by a similar significant decrease in the contralateral anterior insula ($p < 0.05$). In addition, both groups show a significant decrease of the caudate nucleus with the effect being more pronounced in the AIC group ($p < 0.01$, ACC: $p < 0.05$, see **Figure 5**).

Independent component analysis

Using ICA, we identified 33 components of which one is significantly different between groups according to its s-mode ($p < 0.05$, corrected for multiple comparison). This component includes AIC, ACC, and small portions of the occipital and parietal lobes (see **Figure 6**). In addition, we looked for components that exhibit a linear trend over runs and identified one component with slope significantly different from zero for the ACC group ($p < 0.05$, corrected for multiple comparison). This component includes thalamus and parts of the basal ganglia (see **Figure 7**).

DISCUSSION

In the current investigation, we compared the effectiveness in pain regulation using real-time fMRI neurofeedback from two different target regions, notably ACC and AIC. At the behavioral level, both for ACC and AIC feedback, the neurofeedback runs showed a decrease in pain perception with respect to the identical pain stimulation in the localizer runs. However, there was no significant behavioral difference in the direct comparison between ACC and AIC and between runs. Despite the absence of behavioral differences between runs, we found effects in neuroimaging for the two target regions. This observation is in line with the known higher sensitivity of neuroimaging, as compared to behavioral measures, in functional MRI studies investigating subtle effects

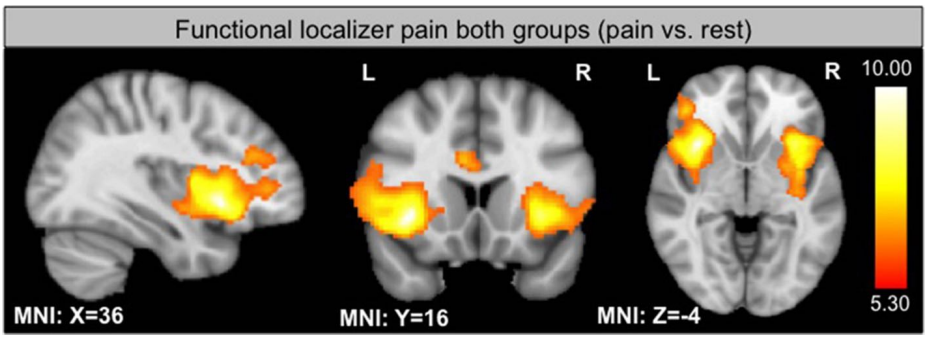

FIGURE 2 | GLM contrast localizer run: pain vs. rest in both groups threshold at $p < 0.05$ FWE.

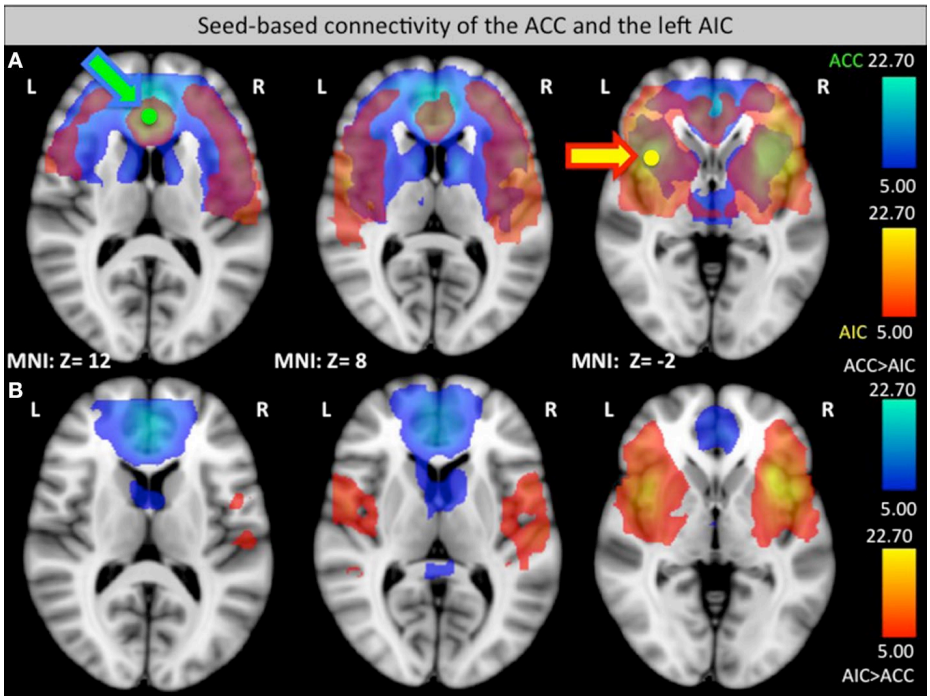

FIGURE 3 | Seed-based functional connectivity of the ACC (green, connectivity blue, A) and left AIC (yellow, connectivity orange, A). (B) Areas that had a significantly greater connection to the ACC than to the AIC (blue) or a significantly greater connection to the AIC than to the ACC (orange) in a direct comparison. Arrows indicate the target seed location.

(Weiskopf et al., 2003; Haller et al., 2005, 2013; Johnston et al., 2011).

At the neuroimaging level, AIC and ACC regulation led to a significant down-regulation of parts of the pain network with practice, notably the caudate nucleus for successful regulators.

Functional-connectivity analyses further demonstrated that both target regions are functionally well connected to other parts of the pain network. Therefore, based on this neuroimaging evidence, we found that both AIC and ACC influence the pain network in a similar fashion through the caudate nucleus.

ACC REGULATION DURING PAIN

Contrary to two previous studies about rt-fMRI ACC regulation of pain processing (Decharms et al., 2005; Rance et al., 2014), we did not find a significant down-regulation effect of ACC regulation over runs within the ACC for all subjects. This might be due to the different experimental paradigm that compared down-regulation vs. no regulation in our setting, while deCharms et al. compared up- vs. down-regulation. Considering that down-regulation might be harder to obtain than up-regulation, as it is easier to explicitly focus on acute pain than to find a strategy to decrease pain, the effect of down-regulation might be smaller. In addition, this particular finding could not be replicated by deCharms et al. in a later follow-up study; as publicly stated at the rt-fMRI conference in Zurich, 2012 (Decharms, 2012). One factor that possibly complicates ACC regulation is that the adjacent anterior mid-cingulate cortex (aMCC) is also thought to be involved in rt-fMRI neurofeedback regulation (Lee et al., 2012), inducing activation during the regulation and thus making it harder to detect the deactivation in nearby ACC, and possibly also confounding the participants' feedback signal itself to some extent. This possible confound is less strong in the recent study of Rance et al. as they used a more rostral part of the ACC leading to a significant down-regulation of this ROI. Therefore, future studies should preferably use a more rostral part of the ACC.

Nevertheless, ACC rt-fMRI neurofeedback did induce a down-regulation of the ACC in a large group of subjects (8/14) as well as a significant change within the caudate nucleus, a brain region involved in planning of goal directed actions (Grahn et al., 2008) and affective processing of pain (Borsook et al., 2010). This part of the basal ganglia is anatomically closely connected to the ACC, with functional relevance, for example, in pain avoidance behavior in monkeys (Koyama et al., 2000). Similarly, previous studies found caudate nucleus involvement when participants suppressed pain (Freund et al., 2009; Wunderlich et al., 2011). Thus, the caudate nucleus, regulated via the ACC, seems to be important in deliberate pain control. This result is supported by the seed-based functional connectivity analysis showing a strong ACC—caudate nucleus interaction and the ICA analysis that revealed a specific component including the caudate nucleus and thalamus that showed significantly decreasing s-modes as a function of runs. These results also indicate that the caudate, the thalamus or a combination of these regions could be considered as suitable targets for future pain real-time neurofeedback studies.

AIC REGULATION DURING PAIN

Similar to the ACC group, AIC down-regulation was not significant when looking at all subjects. This difficulty in AIC regulation

Table 2 | Beta values of the target ROI for all subjects, classification criteria (beta value decrease from run 1 to the average of run 2–4), and classification label (+, regulator; −, non-regulator).

Target ROI	Subject	Beta value				Beta value decrease	Regulator
		Run 1	Run 2	Run 3	Run 4		
AIC	1	0.156	0.097	0.400	0.285	−0.315	−
	2	0.332	−0.077	0.212	0.277	0.584	+
	3	0.436	0.274	0.227	0.162	0.643	+
	4	−0.125	−0.698	0.183	−0.862	1.002	+
	5	0.204	0.006	0.462	0.753	−0.608	+
	6	−0.481	−0.367	0.252	−0.290	−1.039	−
	7	0.325	0.224	0.157	0.201	0.395	+
	8	0.446	−0.099	0.274	0.319	0.843	+
	9	1.093	1.163	0.479	0.822	0.816	−
	10	0.268	0.056	−0.161	0.354	0.556	+
	11	1.026	−0.059	1.022	0.313	1.803	+
	12	0.201	0.104	0.149	−0.155	0.506	+
	13	0.257	0.413	0.825	0.353	−0.819	−
	14	−0.008	0.044	0.246	0.422	−0.737	−
ACC	15	0.1934	−0.0628	−0.1711	0.1088	0.705	+
	16	−0.147	−0.101	0.146	−0.162	−0.325	+
	17	0.072	−0.119	−0.502	−0.182	1.020	+
	18	−0.127	0.072	0.060	0.061	−0.575	−
	19	0.341	−0.379	1.795	−0.455	0.063	+
	20	0.281	0.221	0.178	0.013	0.432	−
	21	0.240	0.847	0.309	0.324	−0.760	−
	22	0.117	−0.071	0.097	0.146	0.179	+
	23	−0.008	0.429	−0.610	0.254	−0.097	+
	24	0.450	0.719	0.874	0.943	−1.186	−
	25	0.223	−0.046	−0.051	0.012	0.754	+
	26	0.713	0.476	−0.020	−0.085	1.766	+
	27	0.153	0.248	0.324	0.309	−0.424	−
	28	1.284	0.116	0.754	1.116	1.866	−

might be explained by competing processes within the AIC. On one hand, the AIC was selected as the target for down-regulation as it is a core component of the network involved in pain processing (Apkarian et al., 2005). On the other hand it is likely to be activated in neurofeedback regulation processes (Haller et al., 2010). In addition, the AIC is involved in many other cognitive processes such as saliency detection (Cauda et al., 2012) and emotion regulation and representation (Singer et al., 2004; Eippert et al., 2007). Due to the regulation procedure, saliency of the visual display (focus on the line and the lower part of the "scale") as well as saliency of the pain stimulus (less focus on pain) could be modulated. In addition, the feedback could induce emotions such as frustration or contentment, thus possibly increasing insula activation, thereby counteracting insula down-regulation. This might also explain why all previous studies only reported reliable up-regulation while voluntary down-regulation of the AIC by rt-fMRI neurofeedback was less successful (Veit et al., 2012). The possible interaction of cognitive and emotional processes within the AIC was also underlined by an fMRI study showing increased reaction times and error rates for cognitively demanding tasks during presentation of painful compared to non-painful pictures (Gu et al., 2013).

However, 9 out of 14 subjects showed a trend to down-regulation of the AIC. In these subjects the ROI analysis also showed a down-regulation of the contralateral AIC. This corresponding contralateral change could be expected, given the bilateral processing of higher-level pain functions and the high connectivity between the left and right AIC as confirmed in the functional connectivity analysis. Additionally, the left and right caudate nucleus showed a down-regulation when comparing the first and later feedback runs. The fact that in both groups successful target region regulation is accompanied by a decrease in caudate nucleus activation underlines its importance in pain regulation.

DIFFERENCES IN THE FUNCTIONAL CONNECTIVITY AND ICA BETWEEN GROUPS

Functional connectivity analysis revealed that the ACC shows a stronger functional connectivity to the caudate nucleus while the AIC is more heavily connected to the ventrolateral PFC. These differences might reflect different pathways of pain regulation. While the ACC might directly influence caudate nucleus activity, the AIC has a stronger connection to higher-level processing via the PFC that in turn might regulate caudate activity.

ICA revealed one functional connectivity ICA component involving the ACC and the AIC that showed significantly lower s-mode values (a measure of effect size) in the ACC group in comparison to the AIC group. This implies that AIC and ACC activity overall was higher in the AIC group. One possible explanation might be that AIC regulation is harder to obtain in the beginning due to competing processes within this brain region. This might lead to an increase in pain processing within the AIC and ACC that is compensated at a later phase when subjects learned down-regulation.

EFFECT OF rt-fMRI ON PAIN RATINGS

In addition to our main goal of comparing two targets for rt-fMRI neurofeedback, we also looked at the pain rating as a function of runs. The finding that pain ratings decreased in neurofeedback runs compared to the localizer run suggests that ACC and AIC down-regulation by means of rt-fMRI neurofeedback decreases pain perception. Two contradictory factors potentially confound the interpretation of decrease in pain perception. Habituation might reduce, while sensitization might increase subjective pain perception despite identical physical stimulation. The observed result of decreased pain ratings in feedback as compared to localizer runs would not be expected from a regular pain study as short-term repeated pain stimulation in general causes sensitization rather than habituation (Drdla and Sandkuhler, 2008; Breimhorst et al., 2012). The same trend was seen in another recent pain real-time neurofeedback study (Rance et al., 2014) where slightly higher pain intensity was applied and pain unpleasantness ratings were compared for the last against the first run, indicating a pain sensitization over run. However, we cannot exclude the possibility that the placebo effect, caused by the neurofeedback intervention, might have confounded pain ratings

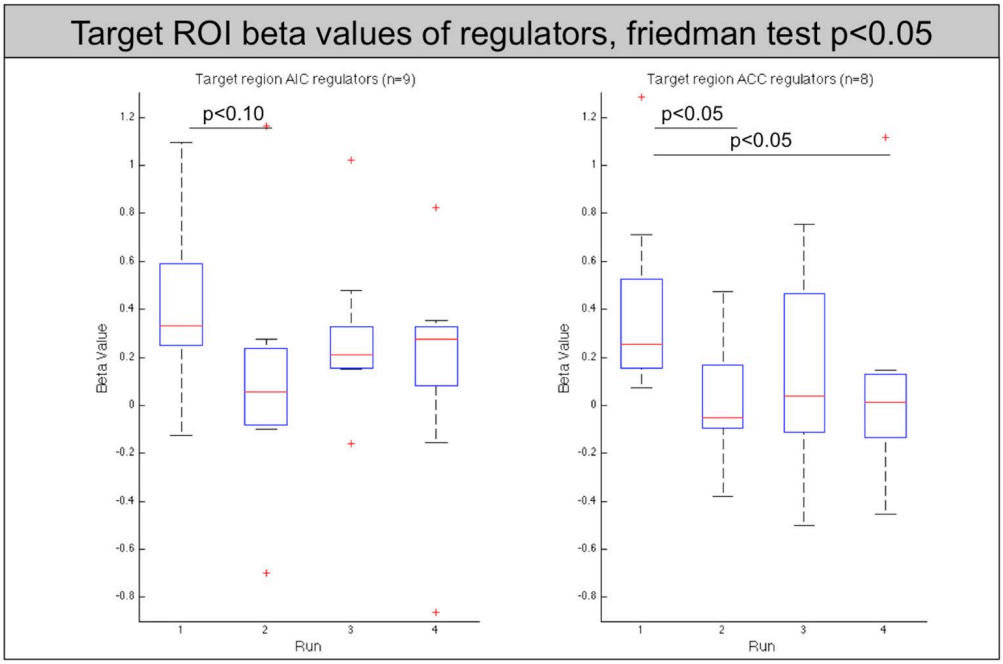

FIGURE 4 | Beta values of the target region (left AIC/ACC) for all regulators across neurofeedback runs (AIC-left, ACC-right). The red line indicates the mean value, the box indicates 25%/75% confidence intervals and the whiskers indicate the most extreme points within 1.5 times of the box length.

Table 3 | Overview of ROIs with their location and *p*-value of Friedman test for change in Beta-value across neurofeedback runs (AIC: $n = 9$, ACC: $n = 8$).

ROI	MNI coordinates			*p*-value—AIC regulators	*p*-value—ACC regulators
ACC	6	20	26	0.115	**0.016**
Left AIC	−34	6	−6	**0.020**	0.415
Left PIC	−38	−20	12	0.086	0.392
Left caudate	−14	−2	14	**0.008**	**0.044**
Right AIC	36	16	4	**0.024**	0.789
Right PIC	40	−16	10	0.091	0.494
Right caudate	16	2	12	**0.026**	0.187

Bold numbers indicate significant results ($p < 0.05$), values for the corresponding target area are highlighted red.

during neurofeedback runs. Pain perception is known to vary depending on the context (Rhudy and Meagher, 2000; Iannetti et al., 2008; Wang and Mitchell, 2011), therefore, making it hard to distinguish the factors that contribute to the pain reduction between localizer run and feedback runs. The fact that subjects were directing attention toward a cognitively demanding task itself could decrease pain perception as shown in a study working with different distraction tasks (Verhoeven et al., 2011). Both effects might be particularly high in the first neurofeedback runs when the task is new and subjects exert more effort than later on, thus possibly counteracting the desired effect of increasing regulation. The difference between localizer and neurofeedback pain rating in the AIC group can also be explained by competing processes within the ROI and the effect of cognitively highly demanding task engagement. These confounding effects might be similar in size to the effects of rt-fMRI, which are expected to be rather small, considering that pain perception has been experienced for years while cognitive modulation of pain has been practiced for minutes only. Some other neuroimaging studies already showed a similar phenomenon: significant neuroimaging effects were not accompanied by corresponding behavioral changes (Weiskopf et al., 2003; Haller et al., 2005, 2009, 2013, 2014; Johnston et al., 2011). This might indicate that objective fMRI data are more sensitive to small-scale changes within a rather small group than subjective behavioral measures. Therefore, it is not surprising that the decreased caudate activity over runs in the AIC and ACC group did not directly lead to a significant decrease in pain rating between feedback runs.

STRENGTH AND LIMITATIONS

The current investigation is a comparison of two possible target regions for rt-fMRI neurofeedback in pain. It clearly indicates that the AIC and the ACC could serve as a pain neurofeedback target in future studies. The following limitations should however be taken into account when interpreting the current results. First, this study did not aim at assessing the absolute behavioral effect of neurofeedback on pain ratings. Thus, further studies including sham feedback as well as modified pain stimulation are needed to separate specific effects of rt-fMRI neurofeedback from habituation/sensitization over time. Additionally, these studies should aim to compare neurofeedback to a sham method with a similar cognitive load, as a high cognitive load could influence pain ratings as well (Verhoeven et al., 2011). Second, as in previous real-time fMRI studies (Decharms et al., 2005;

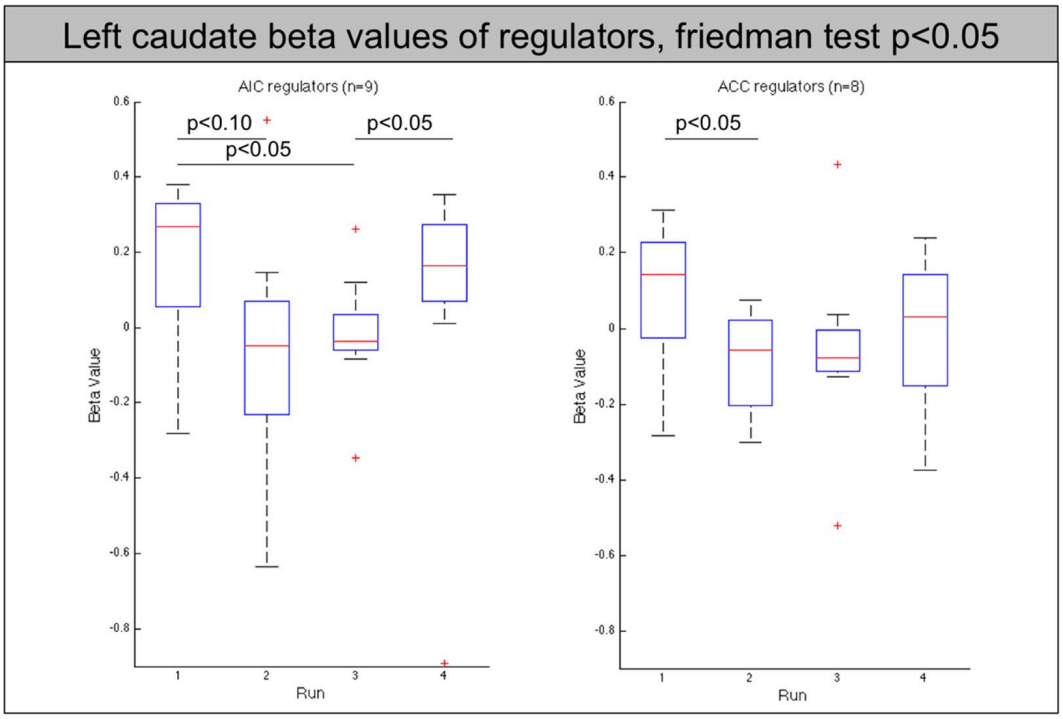

FIGURE 5 | Beta values of the left caudate nucleus for all regulators across neurofeedback runs (AIC-left, ACC-right). The red line indicates the mean value, the box indicates 25%/75% confidence intervals and the whiskers indicate the most extreme points within 1.5 times of the box length.

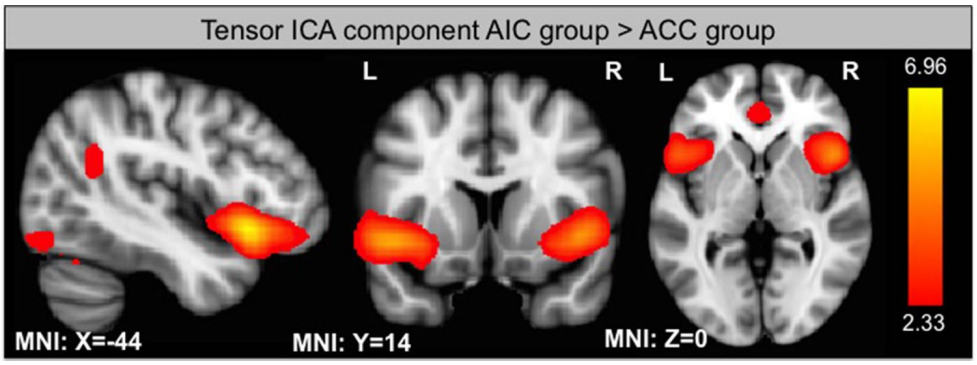

FIGURE 6 | Component from ICA that shows significantly different s-mode values between group.

Bray et al., 2007; Scharnowski et al., 2012; Robineau et al., 2014) not all subjects learned to down regulate the target area. Future studies should aim at identifying the parameters that lead to successful rtfMRI neurofeedback regulation in order to maximize the number of subjects that succeed. Another limitation lies in the use of a GLM on the basis of a box-type function convolved with the hemodynamic response function. Due to this hypothesis about the shape of the response, differently shaped responses such as a decrease in BOLD response after a certain period of pain stimulation, as it has been reported for the thalamus (Tran et al., 2010), would lead to underestimated statistical values.

The ACC and the AIC were judged as the most suitable neurofeedback targets based on literature (see Introduction). Based on our results the caudate nucleus and the thalamus or measures of the connectivity between the ACC and the caudate nucleus (e.g., intrinsic connectivity contrast degree) might be an additional target for future rt-fMRI neurofeedback studies in the domain of pain. As a next step, the potential long-term effects of neurofeedback training on pain perception should be assessed using the AIC, the ACC, thalamus or caudate nucleus as ROI in healthy subjects and as a next step also in chronic pain patients. Due to the possible involvement of the aMCC in neurofeedback regulation processes, the target area should be sufficiently separated

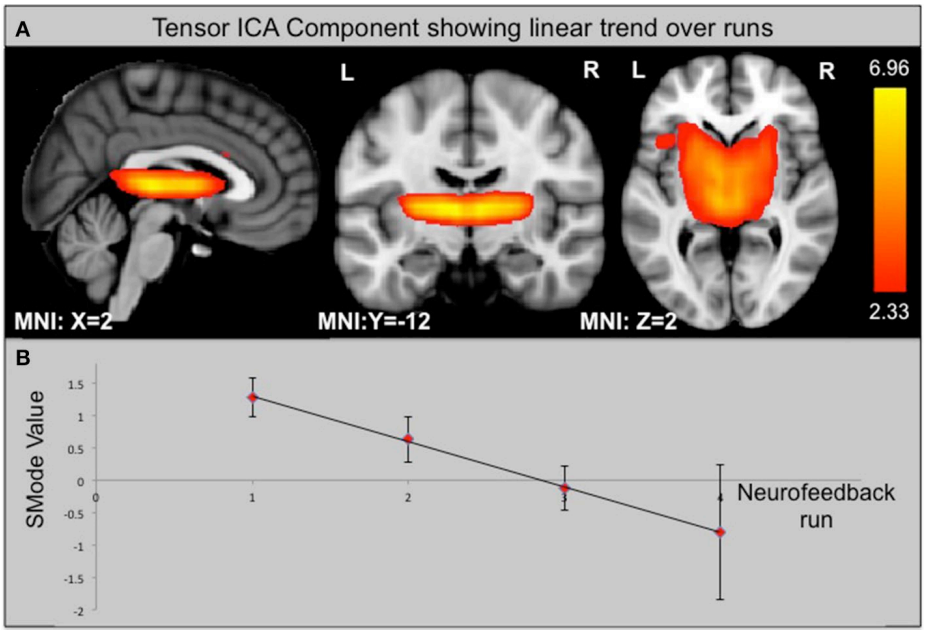

FIGURE 7 | Component from ICA that shows a significant linear trend over neurofeedback runs in the ACC group. (A) Component identified by ICA. **(B)** SMode Values of the component shown in **(A)** over runs. Error bars indicate the standard error of the mean (SEM).

from the aMCC. These future studies could be another important step toward a possible supplemental pain therapy to reduce the impact of pain on patients' life.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnbeh.2014.00350/abstract

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Supplementary Material Publication 2

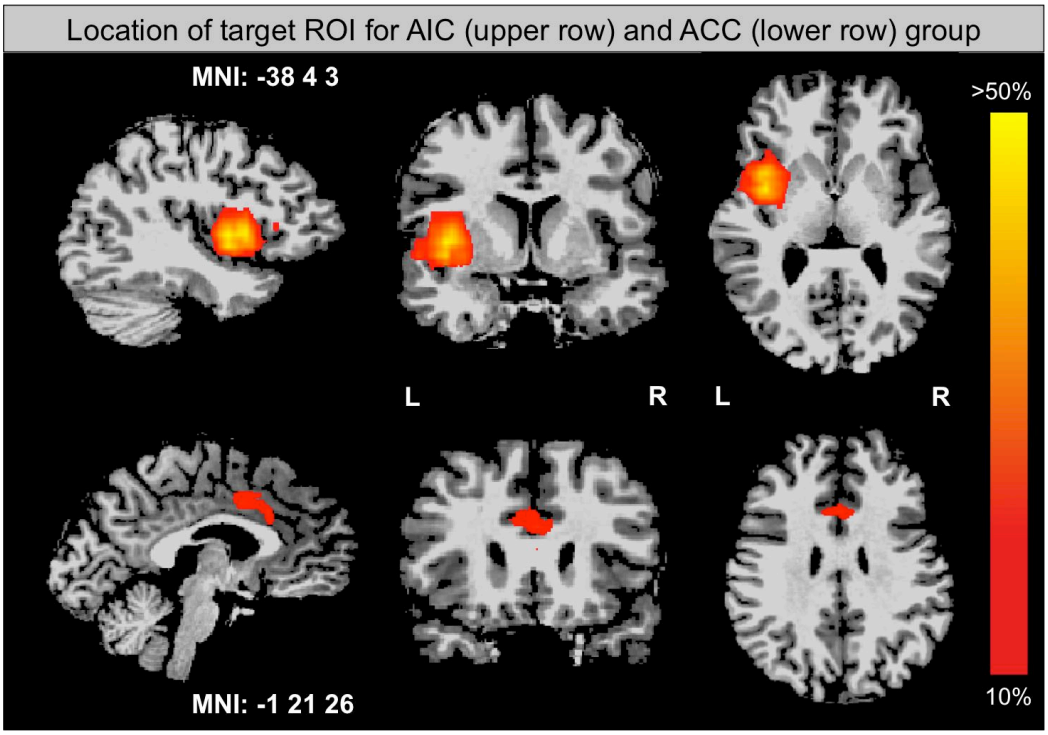
Supplementary material

		ROI -center of gravity (MNI)				
Target ROI	Subject	X	Y	Z	Volume of ROI [mm^3]	Number of voxels
AIC	1	-33.02	4.81	1.84	3267	121
	2	-34.73	5.14	8.75	2565	95
	3	-37.61	12.33	8.19	2943	109
	4	-40.37	8.09	7.40	4131	153
	5	-33.85	4.56	13.95	3996	148
	6	-35.35	-2.63	5.02	3348	124
	7	-35.96	1.82	14.44	4563	169
	8	-32.61	4.44	6.21	3213	119
	9	-44.40	8.34	1.45	3807	141
	10	-33.41	13.02	16.76	729	27
	11	-44.66	0.81	-4.10	1620	60
	12	-29.73	12.96	2.65	2700	100
	13	-31.96	37.04	10.38	2646	98
	14	-38.58	14.73	16.47	1269	47
ACC	15	-4.91	-0.77	39.91	837	31
	16	-7.07	-9.64	39.94	432	16
	17	1.81	7.32	42.84	3159	117
	18	1.27	14.56	38.34	918	34
	19	-0.81	18.52	25.33	1782	66
	20	1.24	12.90	35.17	1755	65
	21	2.53	11.99	30.02	675	25
	22	11.48	17.19	32.31	324	12
	23	6.47	15.75	44.17	1539	57
	24	5.29	20.28	27.03	162	6
	25	4.94	23.35	22.82	378	14
	26	-3.05	27.02	36.14	3510	130
	27	-5.32	0.50	45.29	1863	69
	28	2.03	6.50	44.07	810	30

Supplementary table 1: Location and extent of target ROIs for all subjects.

Supplementary Figure Legends:

Supplementary Figure 1: Group average of location of the target ROIs for the AIC (left) and AIC (right) group.



Supplementary Figure 1: Overlap of the target region per group.

Publication 2 Corrigendum

Due to a mistake in Table 2 we published a Corrigendum on the MIPLab website (https://miplab.epfl.ch/index.php/publications/emmert1402).

There is a mistake in one table of the publication "Comparison of anterior cingulate vs. insular cortex as targets for real-time fMRI regulation during pain stimulation" by Emmert et al., 2014, Front Behav Neurosci 8:350. doi: 10.3389/fnbeh.2014.00350. In table 2 the column "regulator" is partly wrong due to a mix-up of 6 subjects. In addition, the column "beta value decrease" showed 3 times the beta value decrease due to a calculation error. Both of these issues have been rectified in the corrected table below. The mistakes in this table did not affect any subsequent analyses. The number of successful regulators (17 out of 28) remains unchanged and the subject data taken for subsample analyses were correct.

		beta value					
target ROI	Subject	run1	run2	run3	run4	beta value decrease	regulator
AIC	1	0.156	0.097	0.400	0.285	-0.105	−
	2	0.332	-0.077	0.212	0.277	0.195	+
	3	0.436	0.274	0.227	0.162	0.215	+
	4	-0.125	-0.698	0.183	-0.862	0.334	+
	5	0.204	0.006	0.462	0.753	-0.203	−
	6	-0.481	-0.367	0.252	-0.290	-0.346	−
	7	0.325	0.224	0.157	0.201	0.131	+
	8	0.446	-0.099	0.274	0.319	0.281	+
	9	1.093	1.163	0.479	0.822	0.272	+
	10	0.268	0.056	-0.161	0.354	0.185	+
	11	1.026	-0.059	1.022	0.313	0.601	+
	12	0.201	0.104	0.149	-0.155	0.168	+
	13	0.257	0.413	0.825	0.353	-0.273	−
	14	-0.008	0.044	0.246	0.422	-0.245	−
ACC	15	0.193	-0.063	-0.171	0.109	0.235	+
	16	-0.147	-0.101	0.146	-0.162	-0.108	−
	17	0.072	-0.119	-0.502	-0.182	0.340	+
	18	-0.127	0.072	0.060	0.061	-0.191	−
	19	0.341	-0.379	1.795	-0.455	0.021	+
	20	0.281	0.221	0.178	0.013	0.144	+

21	0.240	0.847	0.309	0.324	-0.253	–
22	0.117	-0.071	0.097	0.146	0.060	+
23	-0.008	0.429	-0.610	0.254	-0.032	–
24	0.450	0.719	0.874	0.943	-0.395	–
25	0.223	-0.046	-0.051	0.012	0.251	+
26	0.713	0.476	-0.020	-0.085	0.589	+
27	0.153	0.248	0.324	0.309	-0.141	–
28	1.284	0.116	0.754	1.116	0.622	+

Table 2.1 – Corrected table 2 of the publication "Comparison of anterior cingulate vs. insular cortex as targets for real-time fMRI regulation during pain stimulation" by Emmert et al., 2014. Table 2: Beta values of the target ROI for all subjects, classification criteria (beta value decrease from run 1 to the average of run 2–4), and classification label (+, regulator; –, non-regulator).

2.3 Publication 3

The same neuroimaging data set as used in publication 2 was subsequently analysed in combination with behavioural meta-data in the third publication. The goal was to find behavioural factors that are linked to NFB success. Therefore, we examined pain coping habits of the participants directly prior to their participation in the neurofeedback experiment using the pain coping style questionnaire (CSQ). Does the way people are used to deal with pain in general influence their ability to self-regulate pain-sensitive brain regions? In addition, it would be interesting to see if differences in pain coping style also influence brain processing during neurofeedback. To this aim, we analysed the relationship between neuroimaging data, pain rating and coping style scores. Publication 3 was published in *Brain Imaging and Behavior* (2016 Apr 12., Epub ahead of print).

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ORIGINAL RESEARCH

Active pain coping is associated with the response in real-time fMRI neurofeedback during pain

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Abstract Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback is used as a tool to gain voluntary control of activity in various brain regions. Little emphasis has been put on the influence of cognitive and personality traits on neurofeedback efficacy and baseline activity. Here, we assessed the effect of individual pain coping on rt-fMRI neurofeedback during heat-induced pain. Twenty-eight healthy subjects completed the Coping Strategies Questionnaire (CSQ) prior to scanning. The first part of the fMRI experiment identified target regions using painful heat stimulation. Then, subjects were asked to down-regulate the pain target brain region during four neurofeedback runs with painful heat stimulation. Functional MRI analysis included correlation analysis between fMRI activation and pain ratings as well as CSQ ratings. At the behavioral level, the active pain coping (first principal component of CSQ) was correlated with pain ratings during neurofeedback. Concerning neuroimaging, pain sensitive regions were negatively correlated with pain coping. During neurofeedback, the pain coping was positively correlated with activation in the anterior cingulate cortex, prefrontal cortex, hippocampus and visual cortex. Thermode temperature was negatively correlated with anterior insula and dorsolateral prefrontal cortex activation. In conclusion, self-reported pain coping mechanisms and pain sensitivity are a source of variance during rt-fMRI neurofeedback possibly explaining variations in regulation success. In particular, active coping seems to be associated with successful pain regulation.

Keywords Real-time fMRI · Neurofeedback · fMRI · Pain · Pain coping · CSQ

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Abbreviations

ACC	Anterior cingulate cortex
AIC	Anterior insular cortex
BOLD	Blood oxygenation level dependent
CSQ	Coping Strategies Questionnaire
fMRI	Functional magnetic resonance imaging
GLM	General linear model
MPRAGE	Magnetization prepared rapid gradient echo
NFB	neurofeedback
NRS	Numeric rating scale
PC	Principle component
PCA	Principle component analysis
PIC	Posterior insular cortex
rt-fMRI	Real-time fMRI

Introduction

Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback recently became a popular method to learn voluntary regulation of brain activity. As it is a rather new technique, publications have focused to date mostly on the technical feasibility and validity of the technique and its possible applications in different clinical fields such as chronic pain (deCharms et al. 2005), schizophrenia (Ruiz et al. 2013), tinnitus (Haller et al. 2010) and depression (Linden et al. 2012). Thus, mainly the neuroimaging results and behavioral outcome measures for the examined clinical populations were assessed. However, it is known that neurofeedback efficacy varies considerably between subjects (Johnston et al. 2011; Weiskopf et al. 2003; Emmert et al. 2014), yet the origin of this inter-individual variability remains poorly investigated.

Here, we looked to find domain-specific behavioral factors that influence neurofeedback using previously published neurofeedback data regulating pain sensitive areas (Emmert et al. 2014). Brain areas involved in pain perception include the primary and the secondary sensory cortex and the posterior insula (Peyron et al. 2000; Apkarian et al. 2005; Tracey 2005). Areas involved in pain arousal and emotion, pain consequences and pain modulation include the anterior cingulate cortex (ACC), the anterior insula (AIC), prefrontal cortical areas and subcortical areas (including the basal ganglia and the thalamus) (Apkarian et al. 2005; Friebel et al. 2011). In addition, brainstem structures including the periaqueductal gray (PAG) and the ventral tegmental area are also implicated in perception and modulation of pain by controlling the gain of pain transmission from the spinal cord (Apkarian 2008). It has been shown that pain perception and processing is influenced by a variety of psychological factors. For example, this is evident when looking at the placebo/ nocebo effect that influences pain related brain activation (Bingel 2010; Kong et al. 2008; Lidstone and Stoessl 2007). Two recent meta-analyses on placebo neuroimaging studies showed that expected pain reduction is accompanied by a reduction in dorsal ACC and MCC, insula, thalamus, amygdala, striatum, superior temporal and precentral gyri and lateral prefrontal cortex activation, as well as an increase in activation in the dorsolateral and ventromedial prefrontal cortex, the left inferior parietal lobule and postcentral gyrus, the rostral ACC, the midbrain around the PAG, the left anterior insula, and the striatum (Atlas and Wager 2014; Amanzio et al. 2013).

There are attempts to use the link between cognition and brain activation to alter pain processing through different behavioral strategies including distraction-based techniques, cognitive behavioral therapy and mental imagery (Flor 2014; Jensen et al. 2012). The ACC and the AIC seem to be of particular importance for the perception of pain intensity and affect (Favilla et al. 2014), especially in neurofeedback studies (deCharms et al. 2005). Previous neurofeedback showed successful regulation of the AIC in healthy participants (Lawrence et al. 2013; Caria et al. 2007), obese participants (Frank et al. 2012) and in schizophrenic patients (Ruiz et al. 2013) although up-regulation seems to be easier than down-regulation (Veit et al. 2012). The ACC was mainly regulated in the context of pain studies. A previous pilot study in patients with chronic pain (deCharms et al. 2005) found that anterior cingulate cortex (ACC) regulation using rt-fMRI neurofeedback resulted in a decrease of pain intensity. Further research with healthy participants confirmed that down-regulation of the ACC is possible (Rance et al. 2014; Emmert et al. 2014). However, up-regulation was not successful (Rance et al. 2014) and researchers found that effects of pain regulation through neurofeedback vary between subjects (DeCharms 2012).

In our previous study (Emmert et al. 2014), we compared neurofeedback efficacy during pain using either the AIC or the ACC as the target region. Even though our results suggested that the majority of both groups were able to regulate the target area, the effect size varied substantially between subjects, leading to the hypothesis that there is an unexplained variability during neurofeedback. Concerning pain neurofeedback studies, these differences might be related to how subjects cope with pain in general.

Individual pain coping behavior can be assessed by the Coping Strategies Questionnaire (CSQ) (Rosenstiel and Keefe 1983), a self-reporting questionnaire. The CSQ has been repeatedly applied to healthy subjects in experimental pain studies (Hastie et al. 2004; Lefebvre et al. 1995; Lester et al. 1996; Campbell et al. 2005; Kashikar-Zuck et al. 1997). The active score of the CSQ is of particular interest for brain regulation during pain, as it was shown to predict perceived control over pain (in particular the sub-scale self-statement) (Haythornthwaite et al. 1998) and self efficacy (Keefe et al. 1997). Therefore, we use the CSQ as a tool to investigate the

association between individual coping behavior and brain activity during neurofeedback as a source of inter-individual variability in neurofeedback pain paradigms.

Material and methods

Participants

Twenty-eight healthy subjects (mean age: 27.5 ± 2.3 years, 14 male, 14 female) gave written informed consent to participate in this study that was approved by the local ethics committee of the Rhineland Palatinate medical association in Mainz, Germany. Participants were randomly assigned to two groups of 14 participants each, including seven men and women per group (AIC-Group: 27.6 years ± 2.1, ACC-Group: 27.4 ± 2.6 years). The left anterior insula (lAIC) served as a target region for feedback in the first group while the second group received feedback from the ACC. Exclusion criteria were acute or chronic pain, pregnancy, severe neurological or internal disorders, intake of painkillers and contraindications for MR-measurements. All participants received financial compensation for the study.

Assessment of pain coping behavior

Before undergoing the experiment, all subjects completed the CSQ (for an overview of the CSQ structure see Fig. 1). The score for active coping consists of six sub-scores (diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, increasing activity level, increasing pain behaviors) and is the main behavioral outcome parameter assessing coping strategies. Each sub-score is calculated from ratings of six strategies each (randomly distributed in the questionnaire) and subjects used a 7-point Likert scale ranging from 0 ("never do that") and 6 ("always do this") to rate how often they use or would use each strategy to cope with pain. As an example, the self-statement score is calculated from the six items listed in list 1.

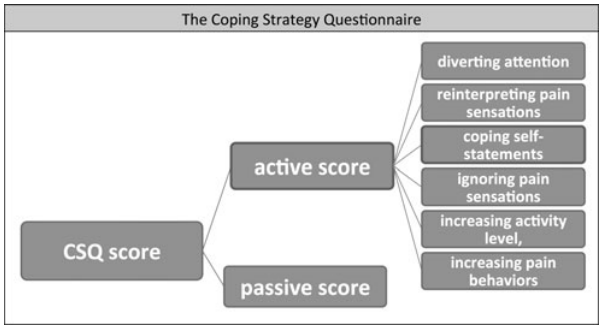

Fig. 1 Structure of the Coping Strategy Questionnaire (CSQ) assessing personal pain coping

List 1: Items of the CSQ self-statement score (extracted from Verra et al. 2006; Rodriguez Franco et al. 2004)

Subjects are asked to rate from 0 (never) to 6 (always) what they do when in pain.
1.) I tell myself to be brave and to carry on despite the pain.
2.) I tell myself I can't let the pain stand in the way of what I have to do.
3.) I see it as a challenge and don't let it bother me.
4.) I tell myself that I can overcome the pain.
5.) No matter how bad it gets, I know I can handle it.
6.) I keep on going although it hurts.

Real-time experiment

For a detailed description of the paradigm the reader is referred to the initial description of this data set (Emmert et al. 2014). Prior to the neurofeedback part of the experiment, a functional localizer ran with an ON-OFF block design of eight blocks alternating between continuous painful heat stimulation for 30 s and rest for 30 s each. This was carried out to identify each individual's target region. Thereafter, the main experiment of four identical neurofeedback runs was conducted. Each run consisted of a block design of four rest and regulation blocks (30 s each) proceeded by 15 s of initial rest before the first block (see Fig. 2). Online data analysis was performed using TurboBrainVoyager (Brain Innovation, Maastricht, The Netherlands, Version 2.8). The target region was chosen based on significant activation within the lAIC/ACC during the functional localizer. During regulation phases, the same pain stimulation as during the localizer was undertaken. In addition, subjects were requested to decrease the target region activation represented by a yellow line. The background color of the yellow line indicated to either keep the yellow line constant (black = rest blocks, no heat pain) or to decrease the amplitude of the yellow line (blue = down-regulation, heat pain). Subjects could freely choose their own mental strategy to decrease target region activation. They were not informed about any link between their task and their pain experience. Employed strategies are summarized in the supplementary Table 1.

Pain stimulation and rating

Pain stimulation was performed using an MR compatible thermode (TSA 2001, Medoc Ltd, Ramat Yishai, Israel) placed on the middle of the right volar forearm. Initially, the thermode temperature was adjusted for each participant to elicit a subjective pain intensity of 7 out of 10 on a numeric rating scale (NRS). In this way, subjective pain was normalized so that pain rating differences towards the end of the experiment would not be caused by differences in pain sensitivity but the experiment itself. The thermode temperature was recorded for 26 out of the 28 subjects. This temperature for

Table 1 Weights of all CSQ active sub-scores for PC 1

Sub-score	Weight (U)
Diverting attention	0.5318
Reinterpreting pain sensations	0.1900
Coping self-statements	0.3361
Ignoring pain sensations	0.5377
Increasing activity level	0.4906
Increasing pain behaviors	0.1955

pain stimulation remained constant throughout the experiment. Pain ratings were obtained after each run (including functional localizer) using a 11-point NRS ranging from 0 (not painful) to 10 (most painful). The success of the neurofeedback was determined based on whether the pain rating decreased after neurofeedback (=success) or not.

fMRI data acquisition

Neuroimaging was performed on a 3 T MRI Scanner (Siemens Tim Trio, Erlangen, Germany) with a 32-channel head-coil. Functional data acquisition used an echo-planar imaging sequence (EPI, TR = 1500 ms, TE = 30 ms, matrix size 64 × 64, 24 slices, slice thickness 3 mm without gap). Additionally, a high-resolution T1-weighted anatomical scan (magnetization prepared rapid gradient echo (MPRAGE), 1 mm isotropic) was used for later co-registration with the EPI images.

Statistical analysis of pain ratings, thermode temperature and CSQ scores

Statistical testing for correlation between thermode temperature, pain ratings and the CSQ measures was carried out in MATLAB 2012b (The MathWorks, Inc., Natick, USA) using Spearman's Correlation (two-sided). Due to the strong inter-dependencies of the six active sub-scales of the CSQ (diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, increasing activity level, increasing pain behaviors), Bonferroni correction would be too conservative to apply (Abdi 2007). Therefore, we undertook a principal component analysis for all subjects and all 6 active score subscales using single value decomposition to identify the first principal component that best represents the participant data of the six active CSQ sub-scales. This measure has the advantage of using the structure of the questionnaire (division into six sub-scales) as well as all subscales to a varying degree.

We then checked for correlation between this first component and pain ratings as well as thermode temperature.

Post-hoc GLM activation correlation with behavioral measures

Off-line analysis was performed with FSL 5.0 (FMRIB Analysis Group, University of Oxford, UK). Functional data was spatially realigned, normalized and smoothed (FWHM = 5 mm kernel) in a first step.

Next, first level neuroimaging results were obtained by fitting a standard GLM regressor to the pain stimulation and neurofeedback blocks (block design described under "Assessment of pain coping behavior section", for details on the main effect of neurofeedback please see Emmert et al. (2014)).

Finally, a voxel-wise regression analysis between the behavioral scores (PC1, pain rating and pain rating change between localizer and neurofeedback runs) and the imaging data (using the contrast of parameter estimates (COPE) files of the first level analysis) was performed using a mixed-effects GLM. The main regressor was the demeaned and normalized (values between −1 and 1) score of interest. To exclude the possibility that group-specific differences drive the effect we added non-explanatory co-regressors that model the neurofeedback group (AIC versus ACC target region).

For the fMRI analysis, voxels with a z-score above 2.3 within clusters that exceeded a multiple-comparison corrected significance threshold of $p < 0.05$ were considered significant.

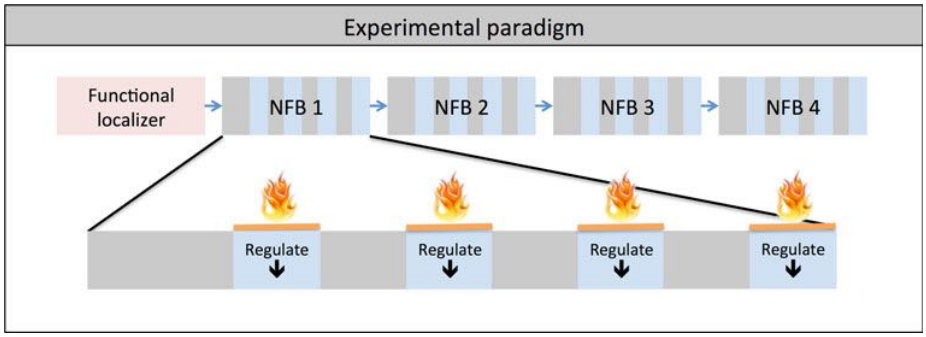

Fig. 2 Experimental design: each of the four neurofeedback runs (NFB) consists of four regulation blocks of 30 s each with pain stimulation

Results

Principal component analysis of the active sub-scores

The principle component analysis (PCA) resulted in a first principal component (PC 1) with only positive weights, indicating that all six sub-scores positively contribute to this component (see Table 1). In particular, these weights indicate how different subscales explain the inter-subject variability (see Table 1). The subscores "diverting attention", "ignoring pain sensation" and "increasing activity level" are most important. Overall, PC 1 is able to explain the majority of the variance (58.57 %).

Behavioral data: correlation of pain ratings, thermode temperature and CSQ scores

There were no significant differences in pain ratings and CSQ scores between the two groups with different NFB target region. Therefore, the analyses in this paper were conducted for all 28 NFB participants together, independent of the targeted ROI (AIC/ACC).

There was no significant correlation between baseline pain rating (after functional localizer) and the first PC. However, the thermode temperature (assessed in 26 out of the 28 subjects) was positively correlated with the localizer pain rating ($R = 0.404$, $p < 0.05$).

The CSQ active first PC and the mean pain rating during neurofeedback runs (average of all 4 neurofeedback runs) yielded a significant (Rho = −0.393, $p < 0.05$, see Fig. 3) negative correlation: participants with a lower first PC had higher pain ratings.

Pain stimulation: correlation of BOLD responses during the functional localizer run with CSQ scores

During the functional localizer run, the first PC was negatively correlated with activation in the caudate nucleus and other neighboring parts of the striatum, the ACC and the lAIC (see Fig. 4). There is no positive correlation of the PC1 with brain activation.

There was no correlation between the thermode temperature and brain activity during the localizer run.

Pain perception during neurofeedback: correlation of BOLD responses during neurofeedback with thermode temperature

Lower thermode temperature for the neurofeedback experiment was correlated with increased activity in the anterior insula and the dorsolateral prefrontal cortex (dlPFC, Brodman area 46) during neurofeedback runs (Fig. 5).

Pain perception during neurofeedback: correlation of BOLD responses during neurofeedback with CSQ scores

When looking at all the neurofeedback runs together, the active scores PC 1 were positively correlated with activation during neurofeedback in the ACC, prefrontal areas (Brodmann areas 9,10) and a small medial part of the left insula. In addition, there was a larger occipital activation, that was more extended on the left side stretching from the hippocampus to parts of the parahippocampal, occipital fusiform (including the peak voxel at −26 −76 −2 (MNI coordinates) with a z-score of 5.03) and lingual gyrus (Brodmann area 19),

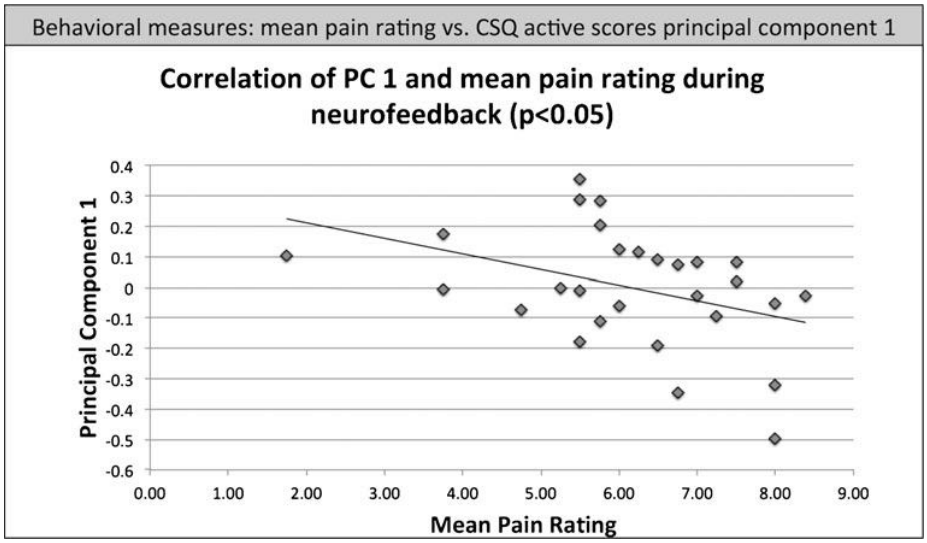

Fig. 3 Pearson correlation of the mean pain rating during neurofeedback with PC1 (Rho = −0.393, $p < 0.05$)

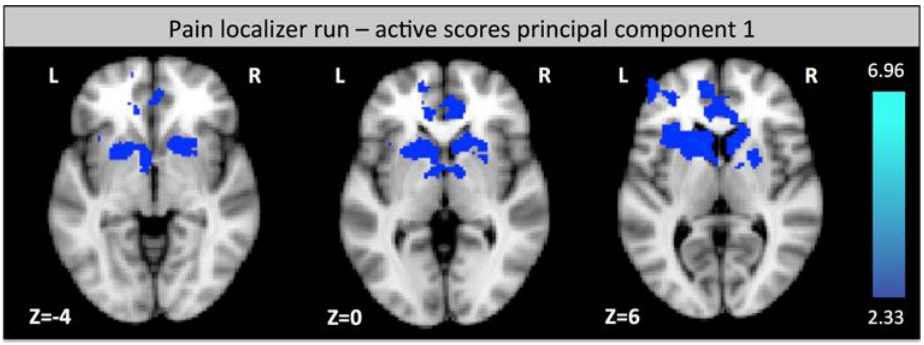

Fig. 4 Brain activation correlation during the functional localizer: activation that is negatively correlated to PC 1 (active coping) during the functional localizer run (z-score > 2.3, cluster thresholding using $p < 0.05$)

encompasing part of the cuneus (Brodmann area 18) and the thalamus (see Fig. 6). No negative correlations were found.

Discussion

Personal pain coping capacity, specifically active coping, was associated with heat pain perception and the ability to influence pain processing with the help of real-time fMRI neurofeedback. During baseline pain, the first principle component of CSQ active sub-scores was associated with deactivation in striatum, ACC and lAIC. During neurofeedback, the PC 1 negatively correlated with the mean pain rating during neurofeedback. In addition, a high PC1 was associated with an increased activation in several brain areas including the ACC, the thalamus and visual areas during neurofeedback.

PCA was successfully used to reduce the dimensonality of the CSQ data, similar to another study looking at CSQ measures in patients with chronic back pain (Woby et al. 2005). Similarly, we excluded the passive measures of the CSQ, including the catastrophizing score, from the coping style analysis, as it does not "represent an effortful response to obtain support or assistance from others" (Woby et al. 2005, page 101). However, while Woby et al. looked at the interaction of catastrophizing and coping habits, we here used the first PC as a summarizing measure of active pain coping. We looked for correlation of this measure with pain rating and brain activity during neurofeedback. Our results show that active coping styles are associated with the success in neurofeedback; i.e., a smaller pain rating compared with participants with a lower PC 1 (as all weights of the PC 1 were positive). This explains the mixed response of subjects to neurofeedback with some showing successful regulation while others did not control their target region activity at all. Therefore, cognitive and personality traits, in particular those related to the regulated area, should be assessed before neurofeedback to preselect those subjects that are more likely to succeed.

Behavioral data: correlation of coping activity, thermode temperature and pain rating

At the behavioral level, we assessed the effect of individual pain coping ability on pain rating during heat pain stimulation and real-time fMRI neurofeedback. We found no significant interaction of the active scores PC 1 and behavior during the baseline pain perception run. This result was expected as the pain stimulus (temperature of thermode) was individually adjusted for each subject to elicit a constant pain intensity (7 out of 10 on a NRS) prior to the localizer run and the participants were not trying to control pain. However, we found a positive correlation of the thermode temperature and baseline pain rating. This is not surprising, as higher thermode temperature should elicit more pain.

The pain during neurofeedback manipulation was negatively correlated to the CSQ active PC 1, indicating that active

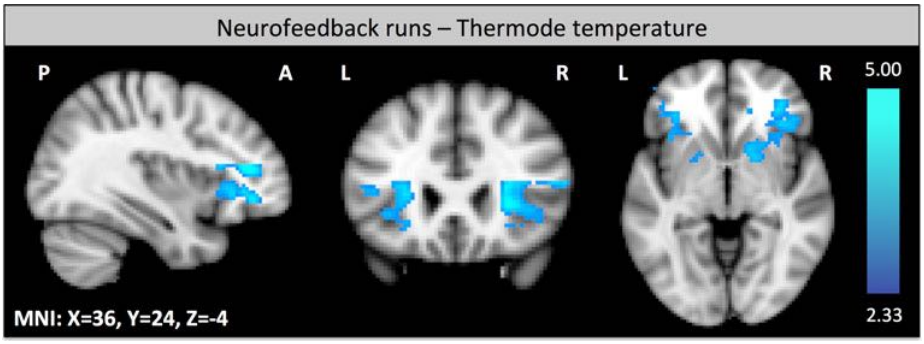

Fig. 5 Brain activation correlation during the neurofeedback task: regions that are negatively correlated with the thermode temperature during neurofeedback runs (z-score > 2.3, cluster thresholding using $p < 0.05$)

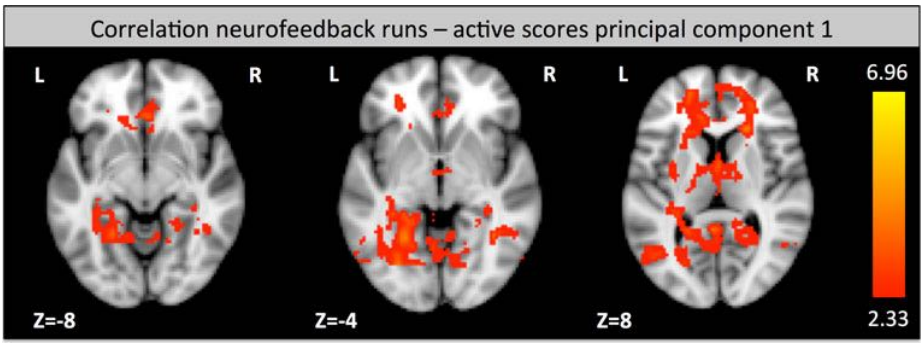

Fig. 6 Brain activation correlation during the neurofeedback task: regions that show a positively correlated activation with PC 1 (active coping) during neurofeedback runs (z-score > 2.3, cluster thresholding using $p < 0.05$)

pain coping may influence pain perception during pain region rt-fMRI regulation.

Correlation of neuroimaging and coping activity during pain stimulation without feedback

In a first step, we assessed brain activation during the functional pain localizer run without neurofeedback. Note that the pain stimulation paradigm was individually adjusted to evoke an individual pain response of 7 out of 10 on a NRS. This means that the subjective pain perception was the same for all subjects in the beginning of the experiment, whereas the actual absolute temperature may have varied between participants.

Despite the fact that the pain stimulation was adjusted to evoke the same degree of subjective pain, participants with a lower degree of active coping had increased activation in the striatum, especially the caudate nucleus, the ACC and the lAIC. This might indicate that pain processing is different in participants that are used to cope actively with pain. This view is supported by a study suggesting that intended pain suppression decreases ACC and caudate nucleus activation (Freund et al. 2007). Furthermore, it has been shown that the use of repeated positive self-statement can increase the pain sensitivity range, i.e. the difference between pain tolerance and threshold (Roditi et al. 2009). Conversely, catastrophizing self-statements sensitized for pain perception (Ruscheweyh et al. 2013). The decreased activity for actively coping participants might be accompanied by an increase in cortisol release, at least for women (Bento et al. 2010).

The fact that brain activation is different depending on active pain coping, even though the subjective pain perception is at the same level, indicates that active coping seems to be associated with the use of different resources during pain. This suggests that there might be a substantial individual variation of how pain is processed depending on the coping habits. A study by Roditi et al. (Roditi et al. 2009) found that the pain threshold remained stable while the pain tolerance (i.e. the time subjects can endure pain) is enhanced in subjects with a higher positive self-statement score. Our results indicate that a less negative/unpleasant perception of pain, indicated by a decrease of activity in pain-interpretation related areas, might be present in actively coping participants in the absence of differences in pain strength. The absence of behavioral effects in the presence of neuroimaging effects can be explained by the fact that pain perception at the behavioral level is influenced by many factors including fatigue, arousal and attention. Neuroimaging data is more directly able to assess subtle changes, especially with small sample sizes, as they are less prone to strong variation depending on these factors. This phenomenon has been observed in various neuroimaging studies, especially when expected effect sizes were low (e.g. Haller et al. 2013; Johnston et al. 2011; Weiskopf et al. 2003).

We found a significant correlation between activation of brain regions associated with pain arousal, emotional processing and modulation and individual active pain coping. Previous neuroimaging studies focused on a passive subscale of the CSQ questionnaire, namely the catastrophizing scale, and found that an increased catastrophizing score is associated with a high response in areas responsible for different aspects of pain (e.g., ACC, claustrum, medial frontal cortex, cerebellum) and motor control (Gracely et al. 2004).

High acceptance scores and low denial scores on a different coping questionnaire were shown to be related to ventrolateral prefrontal cortex activation (Salomons et al. 2007). In contrast to this study, we did not find any positive correlation between brain activation and coping scores. This discrepancy could be caused by the difference of focus of the two different coping questionnaires (pain acceptance versus active coping).

Pain perception, thermode temperature and brain activation during neurofeedback

Thermode temperature (i.e. the intensity of the heat pain stimulus to yield pain rating of 7) was negatively correlated with the activity in the anterior insula and the dorsolateral prefrontal cortex (dlPFC, Brodman area 46) during neurofeedback runs. These results suggests that subjects with a higher pain sensitivity have an increased activity in pain related brain

areas during neurofeedback. This explains why these subjects also show a smaller decrease in pain rating in comparison to the subjects with a lower pain sensitivity.

We also looked at the relation of active CSQ scores to neuroimaging data obtained during all neurofeedback runs. Active coping (high PC 1) was positively correlated with activation of occipital regions involved in vision, especially movement processing, ACC, prefrontal areas, left hippocampus and thalamus activation. One interpretation of the occipital activation is that participants with strong active coping used increasingly vivid mental imagery (Kosslyn et al. 2001) during neurofeedback. ACC and prefrontal involvement might be explained by a conscious effort to suppress pain. In line with this hypothesis, it has been shown that functional connectivity of the prefrontal cortex with the ACC and insula positively correlates with pain measures (Fomberstein et al. 2013). In rats, it has even been demonstrated that prefrontal cortex stimulation induces analgesia (Hardy 1985). Of note, the ACC is part of the pain network contributing to the processing of painful stimuli and part of the brain regulation network (Lee et al. 2012; Ninaus et al. 2013). It seems that among these conflicting processes an increased amount of self-regulation (associated with more active coping) leads to ACC hyperactivity even though pain perception is decreased.

Hippocampus involvement might reflect memory processes, possibly related to mental imagery as a neurofeedback tactic. In addition, thalamic activation might reflect altered somatosensory processing of pain or increased alertness due to more conscious effort exerted during the neurofeedback process for participants with stronger active coping. In total, active pain coping is associated with brain activation during neurofeedback, possibly reflecting a more vivid and dedicated regulation strategy.

Does active coping increase the success of rt-fMRI neurofeedback?

We showed that active coping is positively correlated with regional brain activation during neurofeedback. The negative correlation of pain ratings with active coping PC 1 during neurofeedback runs indicates successful target brain region regulation as pain stimuli were normalized before the start of the experiment. This result is compatible with previous studies showing that positive self-statement predicts self efficacy (Keefe et al. 1997) and perceived control over pain (Haythornthwaite et al. 1998). In summary, active pain coping is associated with success in regulating brain activity.

Limitations

A limitation of this study was the relative small sample size ($n = 28$) used. In addition, further studies are needed to determine whether these results can be generalized to neurofeedback in other domains; i.e., if active coping influences regulation success in general or if this is a specific effect in the domain of pain perception neurofeedback. Moreover, the current study used two different feedback sources (either AIC or ACC), therefore, the sample might be more heterogeneous than studies using only one feedback source for all subjects.

It should be noted that in this study, we are not able to differentiate between the pain regulation abilities independent of neurofeedback, as regulation without feedback was not tested beforehand. Therefore, the pain reduction cannot be attributed unequivocally to neurofeedback training alone. Similarly, we do not take learning mechanisms into account in this study, as the course of neurofeedback learning varies greatly between subjects and no specific model of learning has been shown to hold true for neurofeedback learning yet. Future studies targeting these important questions will help to differentiate between learning, regulation mechanisms and regulation effects. There are also other factors that might influence neurofeedback performance (e.g., intelligence, personality traits). Therefore, future studies with extensive behavioral meta-data are needed to identify all main behavioral influences on neurofeedback.

In addition, it should be noted that this study was conducted on healthy subjects as a first step towards the use of neurofeedback in the field of pain. An external pain stimulus was used as a model for pathologic pain. However, pain processing might differ slightly in chronic pain patients, which should be assessed in a future study. Based on our findings, we hypothesize that behavioral therapy aiming at a more active pain coping could increase neurofeedback efficacy in these subjects as well.

Conclusion

Our results demonstrate that neurofeedback success is associated with individual behavioral traits. Individual coping styles for pain are associated with pain perception and brain activation during rt-fMRI neurofeedback and the regulation success. Future neurofeedback studies should assess which regulation strategies are best suited for subjects with poor pain coping mechanisms to increase their regulation success and therefore to increase the benefit of neurofeedback.

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Compliance with ethical standards

Funding This study was funded by the Swiss National Science Foundation (projects 320030_147126/1, 320030_127079/1 and PP00P2-146318) and by the foundation "Stiftung Rheinland-Pfalz" (Project 936).

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Supplementary Material Publication 3

Supplementary Table 1 Neurofeedback Strategies

Subject	Strategy	Target Region
1	Concentrate on cursor, not pain	AIC
2	Imagination of movement	
3	Mental singing	
4	Increase muscle tension	
5	Fixate a line	
6	Repeat thoughts and words	
7	Try to neglect all feelings of the right arm	
8	Try to move line downward	
9	Calculation	
10	Breathing control	
11	Calculation	
12	Try to conquer pain	
13	-	
14	Progressive muscle relaxation	
15	Try to influence line	ACC
16	Try to perceive pain as less strong	
17	Visualize pushing pain away	
18	Remember poems	
19	Relax through breathing	
20	Attention on breathing	
21	Repeat certain thoughts	
22	-	
23	Breathing control	
24	Breathing control	
25	-	
26	Perceive heat as cold	
27	Concentrate on line	
28	Draw line with the eyes	

Supplementary Table 2 Significant clusters for correlation of BOLD responses during neurofeedback with PC 1 of the CSQ scores (figure 6).

Cluster Index	Voxels	Maximum z-score	MNI coordinates of local maximum			MNI coordinates of center of gravity		
			X	Y	Z	X	Y	Z
2	4189	5.03	-26	-76	-2	-8	-48	0
1	2127	4.77	22	26	6	-2	36	8

2.4 Publication 4

Finally, in the last publication, self-regulation of the auditory cortex in tinnitus patients was used as a model for clinical populations to compare two different feedback presentation timings. One group received continuous feedback that was updated with every fMRI volume acquired, while the second group received feedback only after each regulation period. A previous study looking at a regulation of a motor area in healthy subjects found that intermittent feedback resulted in better self-regulation than continuous feedback [124]. However, it is unclear whether the same holds true for brain-regulation that is not associated with a clear strategy (such as this case of auditory cortex down-regulation). In addition, healthy subjects often differ from patient groups in terms of age and cognitive ability. Therefore, it might be possible that a more direct feedback (i.e., continuous feedback) may be easier to understand and therefore more advantageous for patients. Publication 4 is currently under review at *Neuroimage*.

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

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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 x 3 days). Prior to the neurofeedback, the target region was localized within the auditory cortex using auditory stimulation (1kHz tone pulsating at 6Hz) in an ON-OFF block design. During neurofeedback runs, participants received either continuous (n=7, age 46.84 $\pm$ 12.01, Tinnitus Functional Index (TFI) 49.43 $\pm$15.70) or intermittent feedback (only after the regulation block) (n=7, age 47.42 $\pm$ 12.39, TFI 49.82 $\pm$ 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 the resting-state data and the cerebral blood flow using the 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. In addition, continuous feedback led to a slightly stronger effect over time as compared to intermittent feedback. 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 seems to be superior to intermittent feedback presentation when using the auditory cortex as a target region. In particular, the 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[1]. 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[2–4].

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[5]. Some other studies using intermittent feedback later confirmed that this form of feedback can also be used to elicit significant self-regulation effects[6,7].

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 seconds 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. In addition, 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, healthy and motivated participants, they are not very suitable to make assumptions about the general population and, notably, patients[8]. 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. Tinnitus may substantially reduce the quality of life, particularly when complicated with co-morbidities such as sleep disturbance, anxiety or depression[9]. Tinnitus may occur after a variety of cochlear pathologies, such as acoustic trauma, 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[10]. 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[11,12]. 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[13,14]. Transcranial magnetic stimulation (TMS) of the hyper-activated auditory cortex may improve tinnitus[15–18]. 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 neurofeedback session showed that it is possible to down-regulate the auditory cortex for the majority of six tinnitus patients[19]. In a third 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 used 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 figure 1). Exclusion criteria included pregnancy, severe neurological or internal disorders and contraindications for MR-measurements. All partici-

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

Table 1 Demographic characteristics of tinnitus patients that participated in this study

pants received financial compensation for the study.

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 seconds stimulation followed by 20s 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, [20]).

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 [7,21]). Online preprocessing included motion correction, extraction of the time courses from the region-of-interest, 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 to 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. 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 seconds of rest followed by six blocks of neurofeedback and rest. In the continuous group, one block consisted of 40 seconds of regulation during which the subjects were presented with feedback in form of the moving bar (representing the current activity with respect to the cumulative average across acquired baselines) followed by 20 seconds of rest. In the intermittent group, 40 seconds of regulation without feedback (only the instruction to regulate was shown) was followed by 2 seconds of feedback. Intermittent feedback was calculated as the 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 seconds finished of each block of the intermittent group. The breathing was recorded using Biopac respiration monitoring (RSP100C amplifier, AcqKnowledge version 3.9, Biopac Systems Inc., Goleta, USA).

2.3 Assessment of tinnitus

The tinnitus was assessed by the tinnitus functional index questionnaire (TFI) before, directly after 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.

2.4 MRI data acquisition

Images were obtained from a 3T Siemens Prisma MRI scanner (Erlangen, Germany). 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=1000ms, TE=30ms, 3x3x3mm resolution without gap, 384x384 matrix, functional localizer: 280 volumes, neurofeedback and transfer runs: 390 volumes, resting state runs: 360 volumes). An anatomical image (MPRAGE, TR=2300ms, TE=2.27ms, 1x1x1mm

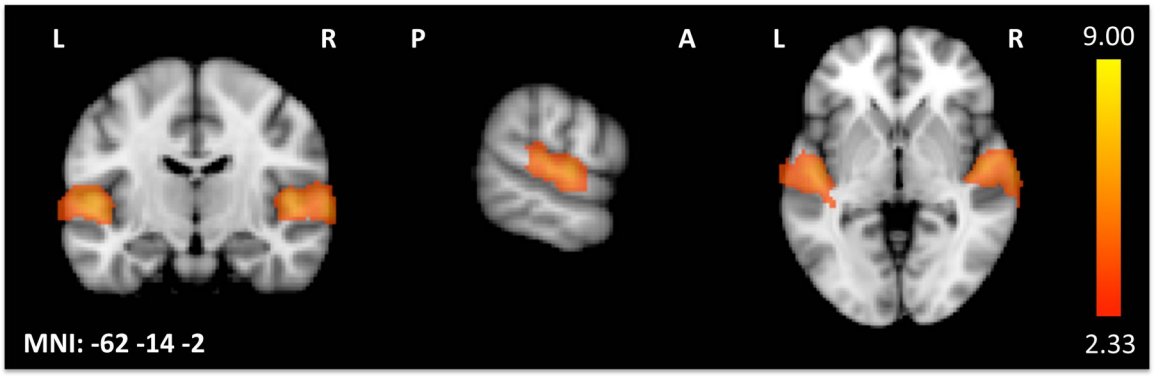

Fig. 1 Main effect of the auditory localizer over all subjects (n=14).

resolution, 256x256 matrix) was obtained for co-registration with EPI images. In addition, arterial spin labeling (ASL) images were acquired at the end of the first and last session (FAIR, TR=4000ms, TE=12ms, TI1=600, TI2=1600, 3.44 x 3.44 x 4 mm resolution, total of 101 volumes (50 tag, 50 ctrl)).

2.5 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 regulation periods for the neurofeedback runs or stimulation periods for the localizer run. 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 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). In addition, unthresholded images masked with the target region are shown as well to illustrate how the effects are spatially distributed within the whole target region.

In addition, 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). 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).

2.6 Resting-state analysis

In addition to neurofeedback runs, subjects also completed two resting-state scans 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 using the auditory cortex, as defined by the functional localizer run, as a seed region was implemented. 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.

2.7 Resting-state analysis

The mean relative cerebral blood flow (relCBF) from the ASL data was automatically calculated by an in-build 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.

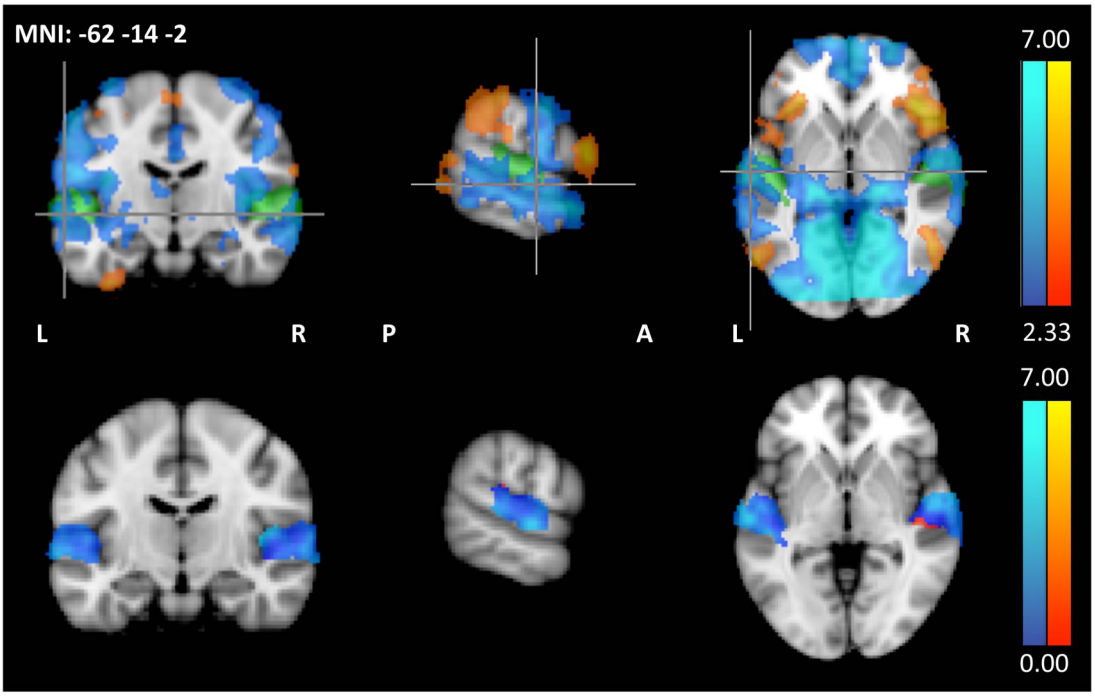

Fig. 2 Main effect of regulation across both groups (n=14). The neurofeedback target region (auditory cortex) is displayed in green in the thresholded analysis in the upper row ($p<0.05$, corrected). The lower row shows untresholded results of the target region for illustration purposes

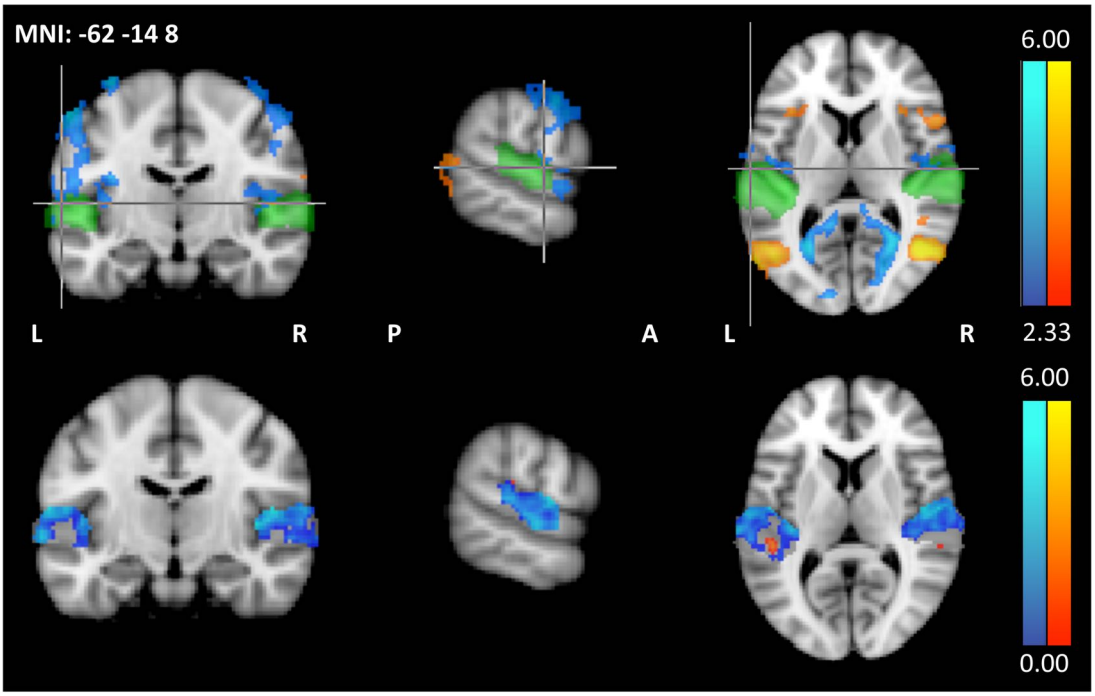

Fig. 3 Conjunction analyses of the continuous versus intermittent FB group of the regulation effect. The neurofeedback target region (auditory cortex) is displayed in green in the thresholded analysis in the upper row ($p<0.05$, corrected). The lower row shows untresholded results of the target region for illustration purposes.

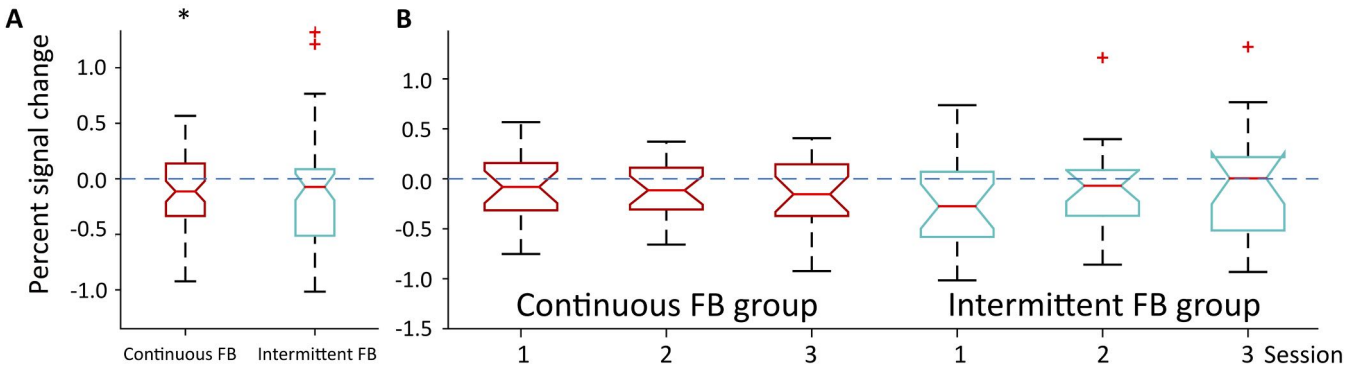

Fig. 4 Boxplots of target region signal change during regulation for the continuous FB group (red) and the intermittent FB group (turquois). A: over all sessions, B: per session.

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 figure 1).

3.2 Neurofeedback runs

The main effect of neurofeedback runs showed that, overall, there was a significant down-regulation of large parts of the auditory cortex (see figure 2). Interestingly, most of the deactivated regions were situated towards the border of the target region (green in figure 2), where the secondary auditory cortex is located. The middle of the target region, where the primary auditory cortex is located, was less deactivated. 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 figure 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 Region-of-interest analysis

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 (p= 0.0046) but not the intermittent group (p= 0.057, see figure 4A). However, when comparing both groups directly, there was no significant difference. Over sessions (see figure 4B), there were no significant effects. 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 not 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 figure 2).

3.4 3.4 Behavioral analyses

The TFI scores did not differ significantly between pre-, post-test and the six weeks follow-up (continuous group: p=0.115, intermittent group p=0.517) though on a descriptive level there is a slight decrease in TFI score (6 out of 7 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 figure 5).

When looking at the sub-scores of the TFI, the relaxation

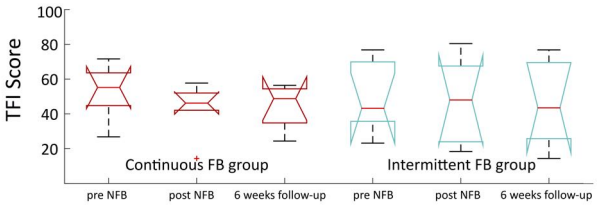

Fig. 5 Boxplots of TFI scores for the continuous FB group (red) and the intermittent FB group (turquois).

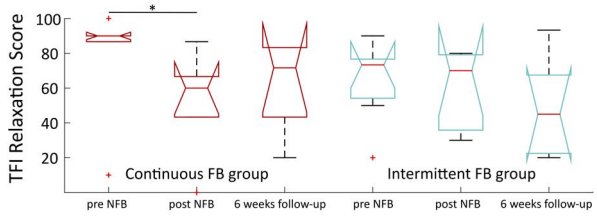

Fig. 6 Boxplots of Relaxation scores for the continuous FB group (red) and the intermittent FB group (turquois).

score (high=relaxation capacity strongly impacted by tinnitus, low= only marginally impacted by tinnitus) was significantly different between the time points (repeated-measure ANOVA, p=0.023, Figure 6) for the continuous group. Post-hoc testing revealed that this effect was mainly driven by the decrease in score between the pre- and the post-FB session (p=0.012). In addition, the difference between the pre-FB session and the six weeks follow-up was nearly significant (p=0.084). No significant differences were found for the intermittent group. When comparing both groups directly, no significant differences were detected.

3.5 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 figure 7). 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, figure S3).

3.6 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).

4 Discussion

Our study demonstrated that continuous feedback is superior to intermittent feedback, notably over multiple sessions when regulating the auditory cortex in a clinical setting. 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[9,22]. A biofeedback study demonstrated that targeting increased relaxation can decrease tinnitus severity in some cases[23]. 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 traditionally involved with emotion processing is increased[24]. 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.

Overall, our results go partially against a previous study on healthy subjects that were regulating the left premotor cortex[5], demonstrating that intermittent feedback improved regulation in comparison to continuous feedback. However, this previous investigation had only one training day. It is important to realize that neurofeedback regulation is a cognitively challenging task, as witnessed by the involvement of a wide-spread neuronal network for the regulation process per se[25]. Performing such a challenging task in a novel environment of a MR scanner is initially difficult, and consequently it is plausible that for the first day the intermittent feedback is 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, also in our dataset, intermittent feedback had a tendency towards a better effect size considering only the first day (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 con-

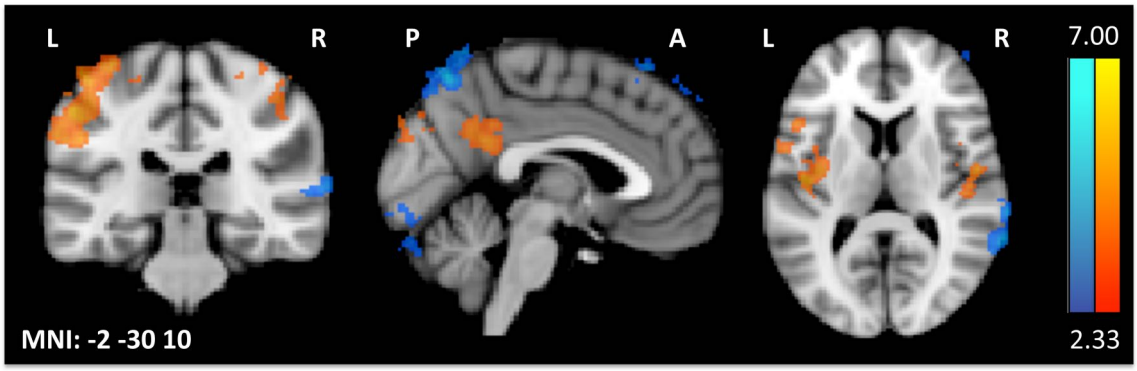

Fig. 7 Effect of session using seed-based connectivity of the auditory cortex (fixed effects analysis). Orange areas show an increased connectivity in the last compared to the first session. Blue areas show a decreased connectivity in the last compared to the first session.

tinuous 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[5]. However, in the long run, continuous feedback provides more details to the participants and consequently had better regulation success in later sessions, and is therefore recommended in particular for clinical applications. Additional differences between the study by Johnson et al. and the current investigation are that in the Johnson et al. study 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[26–28]. 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[29]. If this is true, it is unsurprising that most of the modulation also happens in this affected brain area. In addition, 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.

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[30–32]. It has even been identified as one of the central regions involved in neurofeedback regulation in general[25]. 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[33,34].

No significant changes in cerebral blood flow were detected between the first and the last session 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.

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[35,36]. Therefore, it may well be that we missed a

behavioural 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.

5 Conclusion

In conclusion, our study shows that for self-regulation of a sensory brain region in clinical populations, notably the auditory cortex in tinnitus patients, continuous feedback is more advantageous than intermittent feedback on the long term. In addition, auditory down-regulation increases the relaxation ability for tinnitus patients when continuous feedback is used. These changes 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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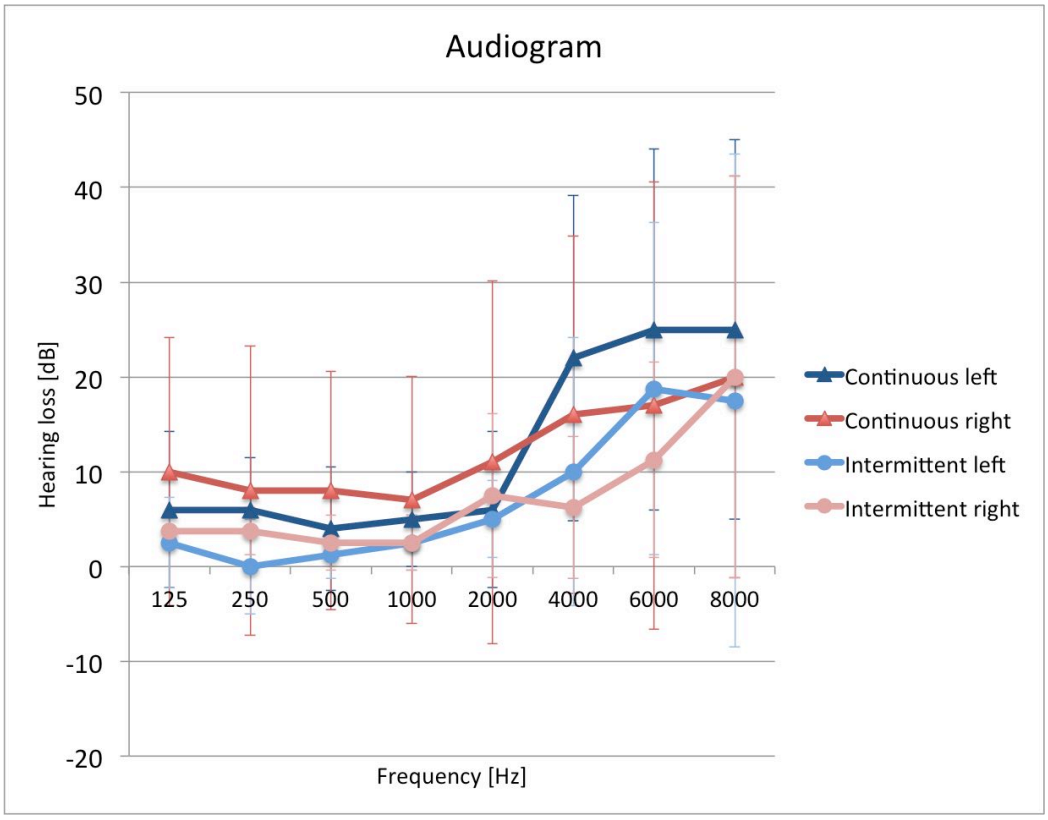
Supplementary Material Publication 4

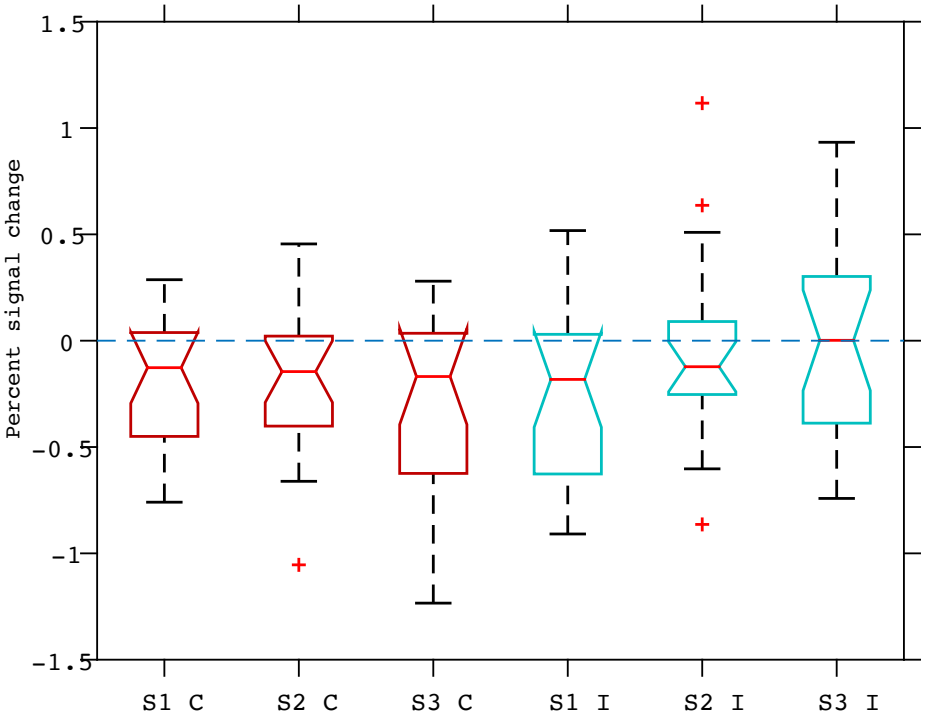
Supplementary Material



Supplementary figure 1: Audiogram from 9 out of 14 subjects (continuous: 5, intermittent: 4).

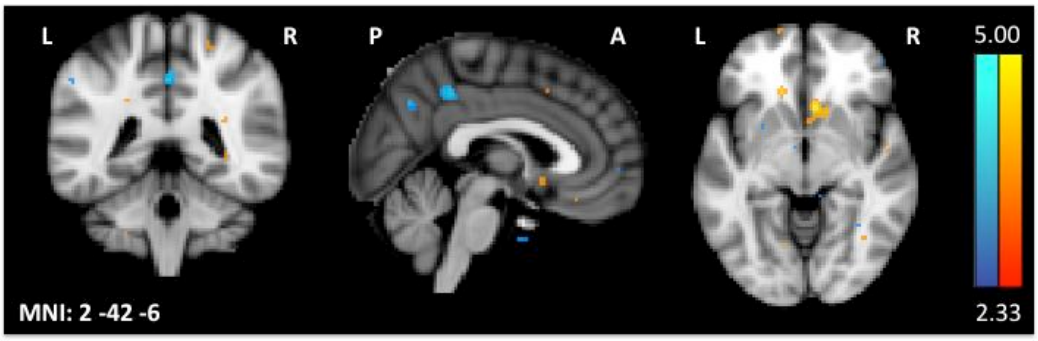
Strategy Suggestions Tinnitus Study

- Try any mental strategy/thoughts that helped to reduce the loudness of your tinnitus in the past.
- Try to relax. Think about a pleasant situation (e.g. the beach you walked down during your last vacation, success at your job, good times you had with your friends or family). Try to experience the pleasant situation as vividly as possible. You could try to recall a certain smell (for the beach example: the smell of the ocean) or positive feelings (how the sand felt on your skin, the warmth of the sun, …). Try not to include sounds in your imagery.
- Try meditation techniques if you know any / Try to detach yourself from any conscious thoughts (“defocus”)
- Try to focus on your body. Become aware of the tension of the muscles in your face or limbs and try to let go of the tension. Feel the sensations created by the vibration of the scanner or your heartbeat. Do not spend too long focusing on any one sensation, but just continue to move your attention around your body
- Try to focus on the bar and imagine it going up.
- Try any other strategy that you might find useful.



Supplementary figure 2: Boxplots of secondary auditory cortex (within the target region) signal change during regulation for the continuous FB group (red) and the intermittent FB group (turquois). S=Session, C=continuous, I=intermittent.

When looking at the contrast of the session effect between the continuous and intermittent group for functional connectivity, no difference could be shown using a mixed effects model. The fixed effects analysis showed small areas within the posterior cingulate cortex where the session effect is smaller in the continuous group in comparison to the intermittent group. In addition, parts of the caudate nucleus showed a stronger session effect for the continuous group.



Supplementary figure 3: Comparison of session effects between the continuous and intermittent FB group using seed-based connectivity of the auditory cortex (fixed effects analysis). Orange areas show an increased session effect in the continuous group. Blue areas show an increased session effect in the intermittent group in comparison to the continuous group.

Overview and Discussion

During NFB, a participant's fMRI measures of brain activity are processed and displayed in real-time to him or her in order to enable self-regulation of brain activity. Research using real-time fMRI NFB has shown that it is possible to self-regulate the activity in brain regions or networks and that this regulation can impact behavioural variables. Most of the early research focused on healthy subjects to understand the neural substrates and possibilities of NFB. The aim was to demonstrate the general feasibility and to show a significant regulation effect. In recent years, the focus shifted towards clinical applications. Here, the purpose is to propose a treatment that tries to decrease the impact of the disorder as much as possible. Therefore, the regulation strength and its effect on behaviour and clinical scores should be optimised.

In the following, I will discuss the specific characteristics of clinical NFB in comparison to normal NFB in healthy participants, how the four publications in this thesis may help to answer important questions in this field and conclude with an overview of recommendations for future studies as well as some suggestions for future research ideas.

3.1 What is different in patients compared to young volunteers?

It is important to take into account the different characteristics of patient groups in comparison to young, healthy participants, as used for the initial NFB experiments. Firstly, patient groups are usually older than healthy volunteers. It is known that many cognitive abilities including working and long-term memory as well as processing speed decline starting from the 20s [284, 285]. Therefore, especially initial patient group

performance may be worse than healthy subject performance. Hence, it might also be useful to test NFB paradigms in older adults as a first step towards clinical applications. Secondly, the disease may impose certain specific restrictions on patients. For example, ADHD patients may complete fewer or shorter runs per NFB session in comparison to healthy subjects due to a lack of focussed concentration. Similarly, chronic pain patients or tinnitus patients with hyperacusis may not tolerate the MRI environment as well as healthy participants. Another factor that is often impacted by the disease is motivation. In certain cases motivation might be decreased as the compensation of disease-specific restrictions may require additional effort. Additionally, in some disorders motivation is directly affect (e.g., in depression). However, the disease burden and the hope for improvement may also increase motivation and compliance in comparison to healthy subjects that are partly motivated by financial incentives. On the other hand, these factors may also lead to an increased placebo effect in comparison to healthy volunteers. Therefore, future studies should also make sure to have suitable control groups when trying to demonstrate a regulation effect in patients. Finally, it should be taken into consideration that while patient groups are a very specific population subgroup, they may be a better representation of the general public in terms of ethnical, educational and political diversity in comparison to typical healthy participants that are often recruited in a research/academic environment and therefore show a bias towards participants with higher education. In this sense, patient studies may give a more realistic estimate of the effect of NFB within the general population.

3.2 How does this thesis help to improve clinical real-time fMRI neurofeedback?

In general, clinical real-time fMRI NFB has demonstrated very promising preliminary results [286]. However, the inter-individual variability of NFB efficacy is high and no double-blinded, randomised, controlled studies or clinical trials are available to prove the general validity of fMRI NFB at the moment. In addition, there have been serious issues replicating an early study with chronic pain patients, indicating the need for strict clinical trials with larger patient groups [56, 209]. Before going into clinical trials, it is important to develop the method so that patients are able to reach a state of reliable, stable and strong self-regulation of the targeted brain region. The stronger the regulation effect, the stronger the beneficial influence on the disease can be expected. In order to see how patients can achieve strong and reliable brain

regulation, I looked at several components within the NFB setup that are important to understand (for an overview of a NFB study and which points are targeted by my PhD work please see figure 3.1) during this PhD work.

1. Which brain regions support the self-regulation process?

The first presented manuscript is a meta-analysis of individual participant data that allowed me to get an understanding about the NFB regulation network by looking at data from several publications with varying characteristics (such as target region, sessions, block length, feedback presentation). The study showed that there is consistent activation of a distributed network of brain areas including the anterior insula, the anterior cingulate cortex and basal ganglia during self-regulation in healthy subjects. The last study in tinnitus subjects and other studies [75, 80] confirm that parts of the same network are also active in clinical populations. The fact that the first publication showed strong basal ganglia activation indicates that self-regulation may indeed follow the dynamics of skill learning. During skill learning, a first phase with a strong learning effect activates the dorsomedial striatum which is followed by a second phase characterised by more gradually improved performance and dorsolateral striatum activation [107]. This was the first study to show which areas are involved in NFB in general. In a next step, it would be interesting to see if activation of some of these areas also correlates with the degree of NFB success.

2. How do different target regions within the pain-sensitive network compare in terms of regulation efficacy?

The second publication helped to determine the influence of the target region on regulation success and the recruited neural resources. The publication focussed on regulation of two targets within the pain-sensitive network, namely the anterior cingulate cortex and the anterior insula, during external painful stimulation. Therefore, the result that both regions are comparable in terms of regulation success is specific to pain real-time fMRI NFB studies. However, target region selection is a global problem of fMRI NFB. In publication 3 we also demonstrated that the two regions interact with other brain regions to different degrees, but achieve similar results, which indicates the variability of possible approaches for target region selection. One could either try to target a specific regulation of a certain area without too much effect on other nodes of the modality specific network; try to look for the best single target within a network that is regulated simultaneously during NFB; or try to directly regulate connectivity within this network. Target region selection in general is very

dependent on the regulated domain. While motor rehabilitation may target rather low-level motor areas, psychological diseases such as addiction may target high-level areas of cognitive control. Therefore, it is important to get a thorough picture of the pathology underlying the disease and how focussed (single region) or more distributed (network) changes could impact it.

3. Influence of personality traits and habits on regulation success

In a follow-up investigation of the same data as publication 2 we determined which habits or personality traits are linked to the regulated domain (i.e., pain in this case) influence regulation success. We were able to demonstrate that people that engage in active coping show a better pain regulation performance. Future studies should therefore test personality traits of participants, in particular, if these are linked to the disease/domain that they are trying to regulate and see whether there is a link to NFB success. In a next step, patients might be pre-selected based on certain personality profiles that have been shown beneficial. It is likely that part of this advantageous personality profile can be generalised for all fMRI NFB studies, while some aspects will be disease specific. In addition, there might also be an interaction between personality profiles and other parts of the NFB setup such as target region selection, which should be taken into account.

4. Influence of the feedback type

Finally, I moved on to a clinical population to optimise the feedback timing. In this study of auditory cortex down-regulation in tinnitus patients, continuous feedback showed better results than intermittent feedback. A reason for this result may be that continuous feedback gives a more direct feedback which allows participants to directly link their short-term thoughts and behaviour with the feedback. Additionally, continuous feedback enables subjects to change their strategy, even within blocks, thereby allowing for more opportunities to explore different strategies. Interestingly, our results are partly in conflict with a previous study showing a stronger regulation effect for intermittent feedback when looking at regulation of a motor area in healthy subjects in one session [124]. A reason for these results might be the absence of feedback and reward processing during regulation in intermittent feedback which reduces distraction. For a single session in healthy populations these advantages could predominate in this kind of setup. Similar results are obtained when only looking at the first session of our data. However, for long-term fMRI NFB studies, continuous feedback seems to be more advantageous, possibly due to the increased

amount of feedback information in comparison to intermittent feedback that may facilitate implicit learning (see publication 4).

Figure 3.1 shows the steps for implementation of a NFB experiment and where the thesis aimed to improve this process (the numbers in red circles indicate which publication helped in which step).

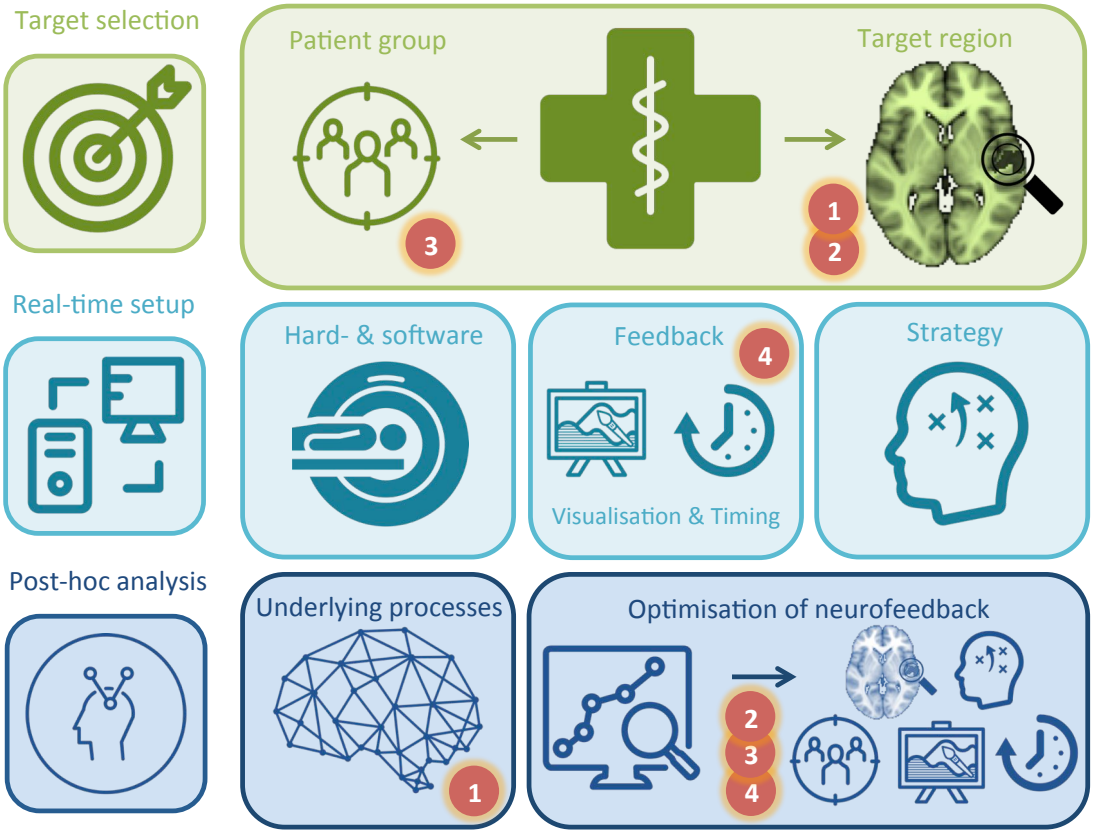


Figure 3.1 – Implementation of a real-time fMRI NFB experiment. The red numbers show the targets of all four publications of this thesis.

(symbols: www.thenounproject.com; designer: Hugo Alberto, iconsphere, Icon Fair, Sergey Patutin, Ralf Schmitzer, Nick Dominguez, Richard de Vos, Delwar Hossain & Chameleon Design)

3.3 Future avenues: recommendations for future studies and outlook

In the following chapter I will discuss the current best practice for real-time fMRI NFB, a few technical aspects that may be helpful in future studies (e.g., multimodal approaches) and future research ideas.

3.3.1 What is the current best practice for clinical neurofeedback?

Neurofeedback signal

Publications 2 and 4 looked at different aspects of the NFB setup in an attempt to optimise them. As described above, the second publication indicates that anterior cingulate cortex as well as anterior insula may be used as target areas for pain NFB studies. However, as both of these regions were later shown to be implicated in NFB per se, it might be more advantageous to try other pain-related brain regions as well. Our study showed that regulation was accompanied by an activation change within the caudate nucleus and thalamus. Therefore, these areas may also be suitable target areas, although they are less robustly activated by pain than the anterior cingulate cortex and anterior insula [287]. In general, there should be a clear hypothesis of a functional abnormality that is causally linked to the targeted disease. This abnormality should be easily detectable using fMRI. As an increasing number of studies also finds changes in connectivity in clinical populations it connectivity feedback may be a good alternative to single region feedback. Recent studies using dynamic causal modelling found that it is possible for subjects to influence functional brain networks (e.g., increase emotional control by increasing top-down connectivity from the dorsomedial prefrontal cortex onto the amygdala) [70, 288].

Neurofeedback presentation

Publication 4 shows that continuous feedback seems to be superior to intermittent feedback when working with a clinical population and a target region without a clear associated regulation strategy. In contrast, another study looking at regulation of the premotor cortex in healthy subjects showed a better performance for intermittent feedback [124]. This indicates that regions that are associated with a clear strategy

(such as motor imagery for the premotor cortex) may benefit from sparse feedback, which is less distracting. To conclude, the feedback presentation timing should be adjusted to the choice of target region.
Concerning feedback display, there is still a lack of studies directly comparing different visualisations. As subjects need to focus on the regulation process per se, feedback should be kept as simple and easy to grasp as possible. In addition, social feedback such as an avatar whose facial expression changes according to the feedback (i.e., smiling if the desired brain activity is reached, frowning when the participant is not performing well) may also be suitable although the current evidence is rather weak [289]. On one hand, this is a rather intuitive form of feedback but on the other hand processing of a social cue also recruits quite a lot of resources, which might interfere with NFB regulation. In addition, including game elements into the feedback may improve motivation and performance. An EEG study showed that by using game elements such as progress bar, level indicator, and a thematic setting in training working memory performance can be enhanced [290]. Therefore, studies comparing different visual representations of feedback should be performed in the future.

Neurofeedback priming: strategy or no strategy?

As indicated in the introduction, it is still unclear whether it is better to provide subjects with an initial strategy or not. However, if subjects are informed about an initial strategy and the purpose of the experiment, it is most likely advantageous to inform them as comprehensive as possible [291]. The aims and objectives of the training should be defined as clearly and as specific as possible [291–293] (e.g. explaining the link between the feedback display and the brain state). In addition, a pre-training session that allows the subject to gain some experience with either the feedback system or train possible mental strategies outside the scanner may be beneficial as well as a practical demonstration of the setup [291,293,294]. If a strategy is provided, it is also unclear which strategy is best. It will certainly depend on the regulated region, but even with the same regulation tasks the best strategy may vary between subjects [295]. Two EEG studies training alpha activity reported that mental strategies related to positive thinking (specifically involving close friends or family) were particularly successful [295, 296]. A recent EEG study demonstrated that SMR, but not Gamma based NFB is influenced by the strategy used [297]. For SMR NFB, people showed greater learning if they shifted from a specific strategy in the beginning towards no particular strategy towards the end of the ten NFB sessions. Among specific strategies, intense concentration seemed to be beneficial [297].

Overview of best practice for neurofeedback today

- Target area/network: preferably not overlapping with the NFB network
- Target area/network: clear hypothesis of a functional abnormality that is causally linked to the disease and ability to visualize this abnormality using fMRI
- Feedback display timing/frequency: depends on target region, continuous feedback seems to be more suitable for clinical applications without a clear regulation strategy
- Feedback display: preferably simple, social feedback (e.g. avatar with facial expressions) may also be advantageous (further studies needed)
- Participant instructions: if instructions are given, a clear aim (e.g. target level), pre-training and/or demonstration of regulation might accelerate NFB learning.

3.3.2 Who is the ideal candidate for neurofeedback?

There is increasing evidence that some candidates show better prerequisites for NFB training than others. One EEG study found that subjects with large grey matter volume and white matter connectivity of the cingulate are better at gaining control over their brain activity [298]. In addition, another EEG study found a strong correlation between the potential for desynchronization of sensorimotor rhythms at rest and BCI performance [299]. Moreover, Scheinost et al. reported that functional connectivity in the orbitofrontal cortex could be used to predict NFB success in OCD patients [87]. Recently, Ninaus et al. demonstrated a correlation of grey matter volume and NFB success for most of the nodes in the NFB network such as insula, prefrontal cortex, thalamus and putamen when regulating sensorimotor rhythms [300], underlining the importance of these areas for NFB. Apart from brain structure and function, behavioural factors may also influence NFB success. So in order to select the candidates with the most potential of benefiting from NFB, it would be good to determine what the key characteristics of a successful candidate are.

As shown in the third publication, NFB success is linked to individual active coping habits that are associated with the regulated domain. There have been other studies (mostly EEG) that also showed an influence of behavioural or cognitive factors on NFB performance. As could be expected, expertise in the modulated modality increases NFB success. For example, trained meditators were better at regulating the posterior cingulate cortex, an area implicated in human awareness, than meditation-naive subjects [63]. Similarly, good visuo-motor coordination facilitates modulation of sensorimotor rhythms with motor imagery [128]. This study also showed that the ability to concentrate on the task is correlated with EEG NFB performance. Another cognitive factor that could influence NFB regulation abilities is memory. Indeed, Daum et al. showed that memory span is correlated to EEG NFB success [301]. Moreover, mood may influence the self-regulation ability. It has been shown that participants that report a positive mood are better at problem solving compared to participants in a neutral or negative mood [302–305]. In accordance with this theory, one EEG brain-computer interface (BCI) study showed that bad mood decreased BCI performance [306]. Additionally, motivation may also influence feedback success. At least for EGG BCI this was confirmed in several studies [306,307]. The role of motivation is also underlined by an experiment in rats showing that the control over cell firing rates rapidly decreased when the reward was diminished or reward contingency was decreased [18]. A NFB study in humans using a motor target area also showed increased self-regulation when a monetary reward was offered [126]. However, it is not clear whether the same holds true for target areas that are not associated with a clear strategy. Interestingly, intelligence does not seem to impact NFB performance significantly [128].

Overview of positive characteristics for neurofeedback training

- Physical (brain structure): large grey matter volume & connectivity of parts of the target region or NFB network
- Behavioural: Active coping, positive mood & motivation
- Cognitive: Expertise, ability to concentrate & greater memory span

Towards individual and holistic patient treatment

These characteristics could help to choose those subjects for NFB studies that promise to benefit most from it. In addition, some of the behavioural and cognitive aspects could be targeted by therapy before or during NFB training. For example, active coping could be enhanced by behavioural therapy (e.g., learn positive self-talk or diverting attention). Therefore, it would be desirable to combine fMRI NFB with (psycho-)therapy in future studies. For example, one could try a holistic approach for disease treatment using pharmacological treatment according to the current gold standard in combination with a long-term psychological and possibly physical therapy (depending on the disease) treatment that includes NFB sessions for suitable patients. In this context, NFB would also help patients to understand the underlying pathophysiology which would in turn facilitate disease coping (e.g., by understanding which behaviours are beneficial and which ones are worsening the disease). In addition, as fMRI has been proposed as a means to objectively assess brain function during individual treatment [308], it would be easy to add NFB to the imaging protocol. Therefore, NFB could be a useful component of an individual patient treatment with an adjustable number of sessions and could thereby support the movement towards precision medicine. This approach does not only provide patients with a better treatment; by pre-selecting the type of treatment individually, costs for ineffective treatments can be avoided.

3.3.3 Is it possible to regulate target areas that are included in the neurofeedback matrix?

Many NFB studies used target regions that are included in the NFB network we found in our meta-analysis, most prominently the anterior insula and the anterior cingulate cortex. This raises the question of whether these areas are really up-regulated by NFB or merely activated by the cognitive effort of trying to regulate. However, just because similar regions are active, this does not mean that the underlying neural processing is exactly the same. Recent studies that looked at activation patterns that are shared and those that distinguish between physical and emotional pain found some response patterns that were unique for physical pain within the right anterior insula [309, 310]. Similarly, successful self-regulation of the insula or anterior cingulate may show a different activation pattern than attempted self-regulation (e.g. with sham feedback). Future studies should therefore look at the specific effect of self-regulation, controlling for cognitive processes during NFB. In this context, it is

especially important to look at studies that also attempt down-regulation of NFB areas as they might need to counteract the activation of the NFB network per se. One study that attempted down-regulation of the anterior insula found that down-regulation could not be achieved within three sessions [311]. In agreement with our results that the anterior insula is implicated in NFB, the no-regulation condition seemed to produce less activation than the down-regulation condition. A pilot study in OCD patients showed fluctuating results for insula down-regulation but overall concluded that down-regulation of the anterior insula is possible [88]. Down-regulation of the anterior cingulate was attempted in a pain study with healthy subjects and chronic pain patients [56]. It seems that they did succeed in down-regulation, although the data only shows the difference between up- and down-regulation conditions, which could also increase purely due to better up-regulation. Other pain regulation studies later confirmed that down-regulation of the rostral anterior cingulate cortex is possible [64, 78]. In the second thesis publication down-regulation of the anterior insula and anterior cingulate cortex was shown to be feasible for the majority of participants (AI:9/14, ACC:8/14). In conclusion, down-regulation of nodes of the NFB network seems to be possible although it is less trivial than up-regulation. In order to facilitate down-regulation of NFB network areas and to dissociate regulation efforts from effects in up-regulation, it might be useful to perform pattern analysis (e.g. multivoxel pattern analysis) to identify patterns that are meaningful for the modality that should be modulated (e.g. pain) but less implicated by self-regulation in general.

Another interesting question is whether self-regulation of different nodes of the NFB network leads to activation of the exact same areas or whether there are some non-target areas that respond specifically to self-regulation of a certain area. The second publication of my thesis showed a comparison of the anterior cingulate cortex and anterior insula as targets. Interestingly, the anterior cingulate showed a more isolated down-regulation with only the left caudate nucleus showing a similar effect. In contrast, the insula regulation showed trends to influence the bilateral posterior insula and had a marginal, though not significant ($p=0.115$), effect on the anterior cingulate as well in addition to a strong effect on the bilateral caudate nucleus. These results imply that, while there are some core components that are active during NFB, other more region-specific areas might also be needed for successful self-regulation.

3.3.4 How can real-time fMRI be used in the context of a multimodal approach?

While fMRI has some advantages such as a good spatial resolution and the fact that even sub-cortical regions can be examined, it also comes with a few drawbacks. These include a poor temporal resolution and comparably high costs. As EEG has inverse properties (high temporal but low spatial resolution) a combination of both modalities promises to circumvent the described disadvantages of both techniques [312]. One study performed real-time fMRI NFB while recording EEG to see the effect of this form of self-regulation on the EEG signal [313]. They found that amygdala up-regulation is accompanied by changes of the frontal EEG asymmetry in the upper alpha band. Another study by the same group demonstrated the real-time NFB of fMRI and EEG simultaneously is possible [314]. Subjects learned to regulate the activation level of the left amygdala as well as the frontal EEG power asymmetry in the high-beta band. The authors mention some advantages of multimodal NFB including the possibility to use training paradigms that need fast self-regulation, the possible optimisation of experimental protocol and strategy based on both feedback signals and regulation of overlapping but slightly different electrophysiological processes underlying BOLD and EEG imaging. However, the regulation of two signals simultaneously may also overstrain patients and therefore future research should look into ways to visualise both signals or combine both signals into one feedback display in the most effective way.

Another approach used fMRI to get an EEG fingerprint of what happens during successful self-regulation using the fMRI signal . Later on, subjects then try to adjust their EEG activity to resemble the fingerprint without MRI [315–317]. This method has the advantage of being cheaper than several sessions of MRI and is also portable, thereby widening the field of possible applications (e.g., treatment at home for post-traumatic stress disorder patients). In addition to EEG, there are other techniques that have a better temporal resolution than fMRI. For example, fNIRS (temporal resolution around 100 ms) could be used in a similar context as EEG in the future (e.g., by acquiring a fNIRS fingerprint of successful real-time fMRI regulation).

3.3.5 What are the next steps in clinical real-time fMRI neurofeedback?

After giving an overview of the results of my PhD work, its implications and the current state-of-the-art in clinical real-time fMRI NFB, I would now like to propose

future work that should be conducted to directly follow-up on my work or answer important remaining questions.

Follow-up work

An interesting follow-up question on the meta-analysis using individual participant data would be to see correlates of successful neurofeedback regulation independent of the target area. Therefore, it would be necessary to have a variable that indicates regulation success. As behavioural variables are often dependent on the regulated area, it would be best to use a more universal success indicator. This could be the achieved activation change in the target area in comparison to a sham condition or group. This variable could then be used to group subjects into successful and not successful regulators and compare their brain activation during regulation. If some areas are found to be more active in the good regulator group, this could later be used to either preselect suitable participants after a screening session or try to train up-regulation of these regions in turn by NFB. For this experiment it would be necessary to get data from NFB studies with different target regions that have a control condition or group.

Considering pain regulation, it will be necessary to find a way to define a target region or network that does not interfere with the regulation process per se. To this purpose it will likely be benefical to use more elaborate ways to extract a feedback signal from the data than simple region-of-interest activity. Suitable techniques may be multivariate pattern analysis or functional/effective connectivity.

When looking at the tinnitus study it would now be useful to conduct a double-blind, randomized study in a large number of tinnitus patients using continuous feedback in order to demonstrate the effect of auditory cortex down-regulation. It may also help to refine the auditory region to those areas that were most prone to down-regulation in the presented study.

Important unanswered questions in real-time fMRI neurofeedback

As the field of real-time fMRI NFB is still in its infancy, there are a lot of unanswered questions. For some of these (e.g. personality traits of regulators, see 3.3.2), it is wise to look into results from the field of EEG NFB which has a much longer history in comparison to fMRI NFB. Here, I am just going to name a few important questions

that should be tackled in the near future to move the field forwards.

What is the best condition for the control group?

In order to address this it would be useful to compare several possible control conditions and see how they perform in terms of fooling the subjects to believe they are actually undergoing NFB and in terms of the degree of frustration after several sessions of sham feedback.

What is the best form of presenting feedback?

To answer this question, it would be useful to compare several feedback modalities (e.g., visual, auditory or tactile feedback) and compare them in terms of success rate. In this context it may also be interesting to see if there is a benefit of providing the feedback in more than one modality simultaneously. As visual feedback is by far the most widespread feedback and is rather easy to implement in an MRI environment, a comparison between different visual presentations would also be advantageous.

How does neurofeedback perform in comparison to other treatment options?

In the long run, it will also be important to see how neurofeedback performs in comparison to other treatments such as cognitive therapy, transcranial direct-current stimulation, transcranial magnetic stimulation or pharmacotherapy. In a first step, it will be necessary to demonstrate the general validity of real-time fMRI NFB in large-scale double-blind, randomised clinical trials before then comparing the different treatment options.

3.4 Conclusion

In my PhD work I addressed some current problems of real-time fMRI NFB for clinical applications. Firstly, I looked at the brain network mediating NFB independently of the regulated brain region and found a core network of NFB comprised most prominently of the anterior insula, anterior cingulate cortex, basal ganglia, prefrontal and visual regions. This network should be taken into consideration when choosing the target brain area or network in future studies. When comparing between two

pain-responsive target regions in a pain NFB paradigm, I found that both regions had similar success rates while recruiting slightly different supplementary brain regions. In addition, success was greater in individuals that tended to cope actively with pain even before the NFB experiment. This indicates that behavioural factors linked to the modality should be taken into account when selecting participants. Finally, a study about the feedback presentation timing revealed that continuously presented feedback produces better results than intermittent feedback in a clinical population of tinnitus patients when the regulated region is not associated with a clear regulation strategy.

In conclusion, I was able to show that real-time fMRI is a complex technique that still offers many opportunities for improvement. By providing some insight into underlying networks, target region selection, influence of behavioural factors and feedback presentation timing, I demonstrated some possible targets for improvement to the clinical real-time fMRI NFB setup. These advances may increase the efficacy of clinical NFB in the future and thus help to establish it as a supplementary treatment for many brain disorders.

Appendices

A.1 Case report: Auditory cortex activation is modulated by somatosensation in a case of tactile tinnitus

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LETTER TO THE EDITOR

Auditory cortex activation is modulated by somatosensation in a case of tactile tinnitus

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Dear Sir,
We would like to draw your attention to some of our recent fMRI findings in a case of volitional tactile tinnitus modulation.

Tinnitus is a subjective auditory perception in the absence of external auditory stimuli. It affects millions of people worldwide [1]. The auditory percept of tinnitus can be continuous or pulsatile. Pulsatile tinnitus is commonly caused by vascular disease. In contrast, continuous tinnitus usually has no identifiable underlying vascular origin. The neural mechanisms underlying continuous tinnitus remain only partially understood, yet neuroimaging of tinnitus has often shown hyper-activation in some parts of the auditory region [2–4].

Many patients with tinnitus have individual strategies to modify the subjective tinnitus intensity, yet the neuronal mechanisms underlying this voluntary modification remains poorly investigated and objectified. Movements that can influence tinnitus include oral facial maneuvers (OFMs) [5], modulation of tinnitus by gazing in a certain direction (gaze-evoked tinnitus, GET) [6], and more rarely tactile tinnitus (also known as cutaneous-evoked tinnitus, CET).

Most known cases of tactile tinnitus (three out of four cases) appeared after posterior fossa surgery [7–9]. Here, we report a thought-provoking case of a patient, who was examined with functional MRI, with tactile tinnitus without prior posterior fossa surgery in whom somatosensory stimulation of the right cheek increases the subjective tinnitus loudness on the right side, yet decreases loudness on the contralateral side.

The patient was a 55-year old right-handed female who reported a tinnitus that could be modified in intensity by tactile stimulation of the right cheek, specifically the dorsal part of the mandibular inferior to the right ear. Interestingly, the subject reported a decrease in tinnitus intensity in the left ear, while the subjective tinnitus on the right increased upon stimulation. At rest, the subject reported a left ear dominant, pulsatile tinnitus at a frequency of 8,000 Hz. The subject's audiogram revealed near normal hearing thresholds. In addition, auditory-evoked potentials were normal as well as a standard electroencephalogram.

Images were acquired using a 3 Tesla Siemens Magnetom Trio Tim scanner (Erlangen, Germany) with a standard 32-channel head-coil. A standard 3-D MP-RAGE sequence was acquired before functional imaging (auditory localizer and tactile task). In order to identify the individual primary auditory cortex region, a standard fMRI auditory block-design paradigm was performed (nine blocks, 20 s on/off) using standard echo-planar imaging (EPI; TR=2,500 ms, TE=30 ms flip angle=90°, 96 by 96 matrix, 39 slices, 3-mm^3 isotropic voxels, interslice gap 0.3 mm, 152 volumes for auditory localizer, 150 volumes for tactile task). Auditory stimulation consisted of a 1,000-Hz sine tone pulsating at 6 Hz that is known to induce a strong blood oxygen level-dependent (BOLD) response in the auditory cortex.

Thereafter, two runs of tactile stimulation were performed in block-design using the same EPI sequence as the localizer. The seven blocks consisted of 25 s of rest (10 volumes, off) and 25 s of tactile stimulation (10 volumes, on) resulting in a run of about 6 min (375 s=150 volumes). During tactile stimulation periods, the subject touched her right cheek

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continuously with the right hand. During rest periods, the right arm rested close to the head without touching it.

The data was analyzed offline employing a general linear model (GLM) using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands) with conventional statistical analysis (type-I error control, false discovery rate at $p<0.05$) [10]. After identifying the region of interest (ROI) with the localizer, areas of activation and deactivation within or adjacent to the ROI were identified. Time course extraction and event-related averaging were performed for the identified areas.

As expected, the auditory stimulation during the localizer task evoked activation in the left and right auditory cortex (see Fig. 1a).

The tactile stimulation data showed an opposed modulation of activation within the left and right auditory cortex. While left ROI activation increased by about 1 % (mean over stimulation period 1.02 %, standard error of the mean (SEM) 0.11 %), right ROI activation decreased by 1 %of BOLD signal amplitude (mean −1.05 %, SEM 0.13 %; see Fig. 2). The increased activation in the left ROI and the decreased activation in the right ROI correspond to the contralaterally perceived increase in tinnitus loudness to the right and decrease of loudness to the left ear reported by the subject.

In sum, we showed that the subjective perception of loudness change could be confirmed by an objective measurement —notably, fMRI BOLD responses within the auditory cortex. The perceived decreased tinnitus loudness on the left side and loudness increase on the right side due to right cheek tactile stimulation is accompanied by a corresponding change in activation in the contralateral auditory cortex. This seems plausible as auditory stimuli are predominantly processed on the contralateral side due to crossing fibers at the brainstem level.

Our study provides convincing evidence that extends previous findings in the literature. In particular, activity in the primary auditory cortex within association areas is modulated by tactile stimulation, showing a change in opposite directions for the left and the right side, while previous work [7] only showed a unilateral change. The involved regions are likely sites of somatosensory-auditory interaction due to multimodal input. As the first reported study was examining a case of strictly unilateral tinnitus including complete unilateral hearing loss due to posterior fossa surgery, results were likely to be biased by this pathology. In contrast, our study looked at a case of bilateral tinnitus with only mild hearing loss, which means that results are more likely to be transferable to normal tinnitus cases. As such, this tactile tinnitus case could suggest a possible model for changes in tinnitus loudness in general; i.e., tinnitus perception is modulated by contralateral auditory cortex activation.

Cross-modal plasticity is a common process, especially pronounced when deprivation of one sensory input system occurs in early ages as in a case of a congenitally deaf human adult who responded to vibrotactile stimulation with activation of somatosensory and auditory regions [11, 12], thus underlining the possible neuroplastic changes between somatosensory and auditory regions. Processes that were hypothesized to account for the increased cross-modal interactions are neuronal sprouting in reaction to neuronal damage (especially in cases with posterior fossa surgery) and unmasking of silent multimodal synapses.

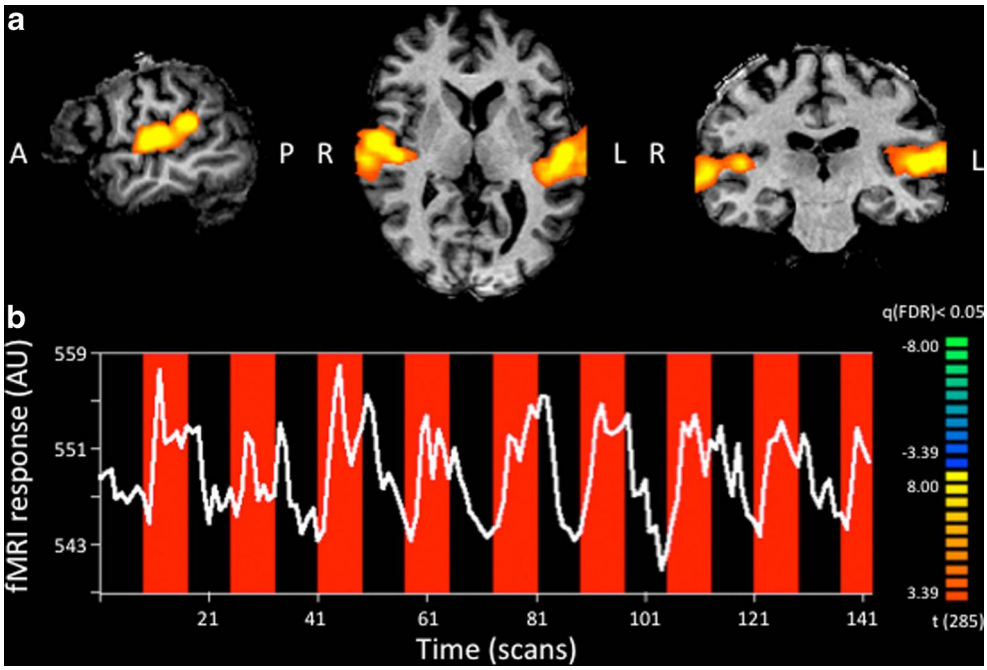

Fig. 1 Regions of interest. **a** Analysis of the functional auditory localizer run resulted in detection of significant activation (*orange*) in the left and right auditory cortex. The activation clusters were used as ROI definitions for analysis of the tactile stimulation run. **b** ROI-averaged time course for the auditory localizer task

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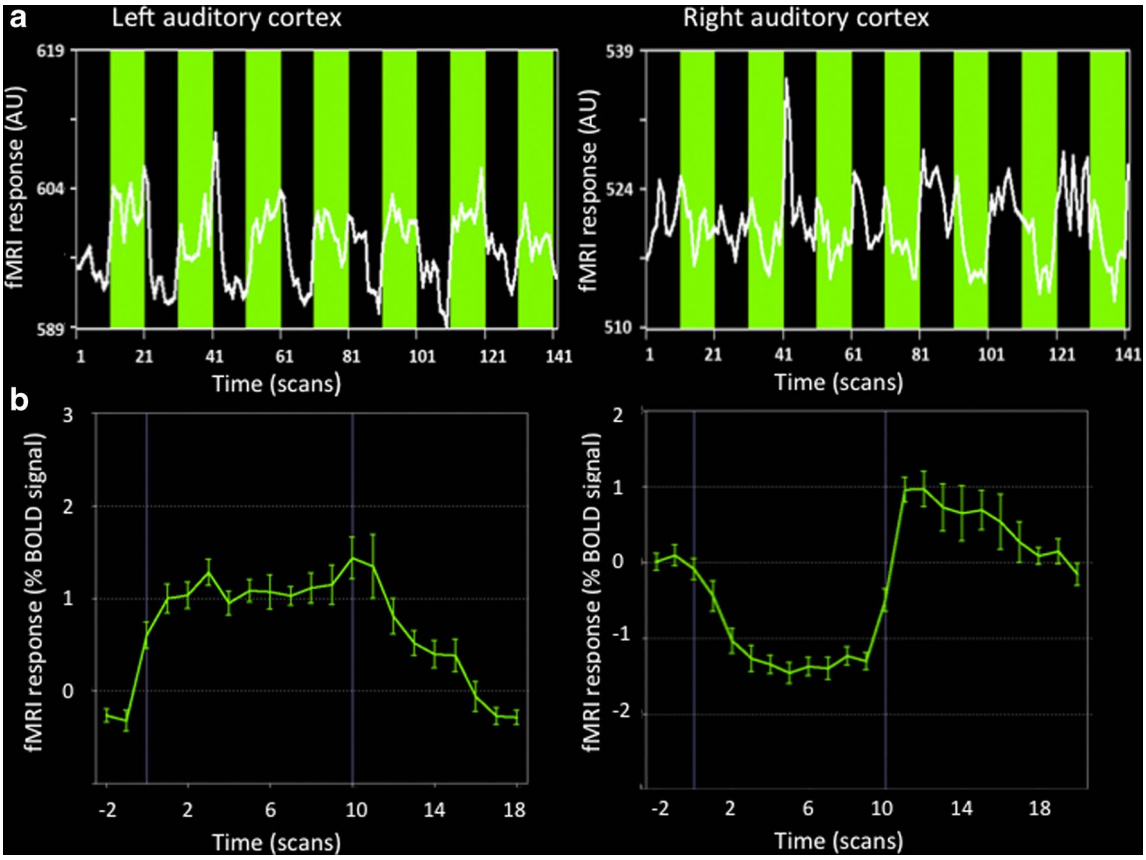

Fig. 2 Results for the tactile stimulation task. **a** Time courses of left and right auditory cortex activation (Talairach coordinates ±57, −4, −1) during right cheek tactile stimulation close to the identified primary cortex. A clear increase during tactile stimulation (*green*) can be seen for the left ROI while there is a deactivation during stimulation for the right ROI which is also reflected in the average time course of all stimulation blocks. **b** Epoch-averaged BOLD responses where *error bars* indicate the SEM

Future research is needed to test how different brain areas are involved and interact in tinnitus modulation. More general studies of tinnitus show increased auditory cortex activation during tinnitus perception (e.g., [13]), which is in accordance with our results as increased loudness also led to an increase in activation in part of the auditory cortex. Due to the very small number of reported cases (5) and the even smaller size of individuals that underwent functional imaging (2), it is difficult to assess which mechanisms and areas could be involved in tactile tinnitus modulation. Moreover, detection power is low and activation differences in very restricted areas such as brainstem nuclei or the medial geniculate body could not be detected so far. In general, an involvement of the dorsal cochlear nucleus and extraleminiscal pathways seems possible for tactile tinnitus modulation while the somatosensory influence on the vestibular nucleus seems to be concentrated on eye movements [14, 15]. As this case reported a tinnitus modulation caused by touching of the cheek, interactions of the trigeminal nerve with the auditory system would also be plausible.

Whether the modified auditory cortex activation is the origin of tactile tinnitus modulation or whether it is only mediating the effect remains to be determined. Due to the small number of patients with tactile tinnitus, a multi-centered, large-scale search for other cases would be needed to set up a functional imaging study with a sufficient number of patients. To assess possible habituation effects of repeated tactile stimulation, as described for a GET case [16], a longer experiment with several fMRI sessions would be interesting. Functional imaging could be used to see if habituation is accompanied by a decrease in activation changes in the auditory network due to tinnitus modulation.

In conclusion, we found objective alterations of neuronal activation related to the subjective modification of tinnitus symptomatology in a case of tactile tinnitus. This observation might be useful when looking at other tactile tinnitus cases, as it might be possible to find objective correlates of their subjective tinnitus modulation as well as ultimately aiming at an objective diagnostic tool for tinnitus modulation. Importantly, the results of this study suggest that a decrease in auditory cortex activation is accompanied by a reduction in tinnitus emphasizing the importance of targeting the central auditory system activation in future tinnitus therapies. Due to the very small number of eported cases in particular implementing functional imaging, future research is needed to validate these findings and identify underlying mechanisms of somatosensory-auditory interactions.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the Commission cantonal d'éthique de la recherche and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that the patient gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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A.2 Glossary

AC	auditory cortex
ADHD	attention deficit hyperactivity disorder
BOLD	blood oxygen level dependent
DCN	dorsal cochlear nucleus
EEG	electroencephalogram
EMG	electromyography
fMRI	functional magnetic resonance imaging
fNIRS	functional near infrared spectroscopy
GLM	general linear model
IC	inferior colliculus
MEG	magnetoencephalography
MRI	magnetic resonance imaging
NFB	neurofeedback
SFR	spontaneous firing rate
SMR	sensory motor rhythm

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