Meta analysis of real-time fMRI neurofeedback studies: how is brain regulation mediated?

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*Abstract*

An increasing numbers of studies using real-time fMRI neurofeedback demonstrated that successful regulation is possible in various brain regions. Since these studies focused on the regulated region(s) themselves, little is still known about the underlying neuronal mechanisms that control brain activation. Single-study results are not suitable to detect self-regulation specific activations, as it is impossible to distinguish them from target region specific activations. In an effort to detect regions that are responsible for brain regulation per se, we performed a meta data analysis of data from different target regions and research groups.

We included twelve suitable studies+ looking at eight different target regions in 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, a higher-level mixed effects analysis including all subjects of all studies was performed.

The GLM analysis revealed that the anterior insula as well as the basal ganglia were consistently active during the regulation of brain activation across the studies. The anterior insula is known to be implicated in interoceptive awareness of the body and basal ganglia are involved in procedural learning and other higher cognitive processes including motivation.

In conclusion, we demonstrate that the anterior insula and the basal ganglia are activated during self-regulation in real-time fMRI neurofeedback independent of the targeted region of interest. Future research is needed to determine how regulation-related activation of the anterior insula might interfere with its use as a target region for real-time fMRI neurofeedback and how activation within the regulation network is related to neurofeedback success.

Keywords: Neurofeedback, real-time fMRI, brain regulation.

Introduction

Neurofeedback using real-time functional magnetic resonance imaging (rt-fMRI) enables subjects to obtain voluntary control of various brain regions. Studies using this technique demonstrated that it is possible to successfully manipulate brain areas including the anterior cingulate cortex -ACC ([Weiskopf et al., 2003](#_ENREF_37)), the posterior cingulate cortex ([Brewer and Garrison, 2014](#_ENREF_4)) ,the anterior insular cortex- AIC ([Caria et al., 2007](#_ENREF_7);[Caria et al., 2010](#_ENREF_6)), posterior insular cortex- PIC ([Rance et al., 2014](#_ENREF_29)), Amygdala ([Posse et al., 2003](#_ENREF_26)), primary motor and somatosensory cortex ([Yoo and Jolesz, 2002](#_ENREF_39)), premotor area ([Johnson et al., 2012](#_ENREF_16)), visual cortex ([Shibata et al., 2011](#_ENREF_33)), auditory cortex ([Yoo et al., 2006](#_ENREF_40)), substatia nigra/ventral tegmental area ([Sulzer et al., 2013](#_ENREF_36)) and inferior frontal gyrus ([Rota et al., 2009](#_ENREF_30)).

Real-time fMRI neurofeedback has even proven to be beneficial as a supplementary treatment for diseases such as schizophrenia ([Ruiz et al., 2013](#_ENREF_31)), depression ([Linden et al., 2012](#_ENREF_21)), tinnitus ([Haller et al., 2010](#_ENREF_13)), Parkinson’s disease ([Subramanian et al., 2011](#_ENREF_35)) and nicotine addiction ([Canterberry et al., 2013](#_ENREF_5);[Hartwell et al., 2013](#_ENREF_15);[Li et al., 2013](#_ENREF_20)).

All previous investigations focused on the effect of neurofeedback on the activation strength within the targeted region of interest. In contrast, it remains unexplored which regions within the brain mediate the voluntary regulation of brain activation. Studies using a single region of interest suggested involvement of the dorsolateral and ventromedial prefrontal cortex ([Haller et al., 2010](#_ENREF_13)) and the anterior mid-cingulate cortex ([Lee et al., 2012](#_ENREF_18)) in the regulation process per se. However, these studies did not explicitly explore the brain network responsible for feedback regulation.

In the current investigation, we specifically assess the brain network mediating regulation in rt-fMRI neurofeedback. We assume that regardless of the target region, the same brain network is involved in the regulation per se,. Consequently, we performed a meta analysis across multiple previously reported rt-fMRI neurofeedback studies with different target regions. In particular, we hypothesize that when analyzing multiple studies with different target regions, activations related to regulation must be consistent and, therefore, remain, while target-region-specific effects will cancel out.

Material 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.ch) literature updates. This search provided us with a total of 316 publications. Next, we used the following selection criteria:

1. Real-time fMRI neurofeedback
2. 1.5 or 3 T
3. Only healthy subjects
4. At least four subjects
5. At least three neurofeedback runs

28 studies complied with these criteria and we therefore contacted the corresponding author. In total, 12 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), 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.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Target area | N | Sessions | Runs per Session | Regulation | External stimuli | Blocks per run | Length of block [s] | Type of localizer |
| **Berman et al. (2011)** | **1°Motor Cortex** | **10** | **1** | **3** | **UP** | **-** | **5** | **20** | **functional** |
| **Berman et al. (2013)** | **rostral Insula** | **13** | **1** | **4** | **UP** | **-** | **4** | **30** | **functional** |
| **Brühl et al. (2013)** | **Amygdala** | **6** | **4** | **2-3, total: 8-11 runs** | **DOWN, NO** | **visual (pictures)** | **10** | **20** | **functional** |
| **Hui et al.. (2014)** | **Premotor Cortex** | **12** | **1** | **4** | **UP** | **-** | **7** | **30** | **functional** |
| **Johnston et al. (2010)** | **VLPFC, IC, others** | **17** | **1** | **3** | **UP** | **-** | **12** | **20** | **functional** |
| **Paret et al. (2014)** | **Amygdala** | **16** | **1** | **3** | **DOWN** | **visual (pictures)** | **15** | **24-26** | **functional** |
| **Robineau et al. (2014)** | **Visual Cortex (interhem. balance)** | **14** | **3** | **4** | **UP (one hemisphere stronger than other one)** | **-** | **3** | **30** | **functional** |
| **Sulzer et al. (2013)** | **SN/VTA** | **15** | **1** | **3** | **UP** | **-** | **9** | **20** | **anatomical** |
| Emmert et al. (2014) -AIC | anterior Insula | 14 | 1 | 4 | DOWN | pain | 4 | 30 | functional |
| Emmert et al. (2014) -ACC | ACC | 14 | 1 | 4 | DOWN | pain | 4 | 30 | functional |
| Frank et al. (2012) | anterior Insula | 21 | 2 | 3 | UP | - | 7 | 30 | anatomical |
| Haller et al. (2013) | Auditory Cortex | 12 | 4 | 4 | DOWN | auditory | 4 | 58 | functional |
| Veit et al. (2012) | anterior Insula | 11 | 1 | 3 | UP, DOWN, NO | visual (pictures) | 6 | 9 | functional |

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.

Analysis of MRI data

A standard mixed effects general linear model (GLM) analysis in FMRIB Software Libary (FSL 5.0.6, FMRIB, Oxford, UK) ([Smith et al., 2004](#_ENREF_34)) was conducted. Preprocessing using standard parameters was performed (motion correction, co-registration, normalization to Montreal Neurological Institute (MNI) space, smoothing using a 5mm kernel).

The first level analysis used the individual study’s block design as a regressor to model neurofeedback blocks. On 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](#_ENREF_38)) 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 twice- with and without coding for the different studies as non-explanatory co-regressors. As there were no relevant differences between the analysis with and without co-regressors, we report only the results of the latter analysis.

Due to the restricted brain coverage of some studies we performed this analysis two times. The first analysis used the whole data set and the restricted field of view covert by all 175 subjects. The same analysis was repeated with a subsample of 8 studies and 103 subjects (first 8 lines in table 1) aiming at a large field of view. All resulting activations were multiple-comparison corrected using voxel-based thresholding at p<0.05.

Results

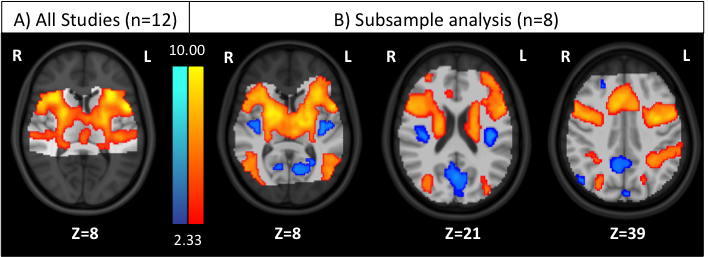


Figure 1: Main effect of the third level mixed effects analysis. (A) Results from the main analysis using all 12 studies (B) Results from the subsample analysis of eight studies with a larger field of view.

The third level mixed effects analysis of all 12 studies yielded two main regions that are consistently activated during neurofeedback: the 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 ventrolateral prefrontal cortex (vlPFC) and an area in the dorsolateral prefrontal cortex (dlPFC) reaching to the premotor cortex (PMC), a large temporo-parietal area and lateral occipital areas including visual association areas and the temporo-occipital junction. In addition, the analysis with 8 studies showed additional brain areas that are less active during neurofeedback, including the posterior cingulate cortex (PCC), the precuneus and the transverse temporal area.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Activations | | | | |
| Cluster | Area | MNI coordinates | | |
| X | Y | Z |
| 1 | pACC | 6 | 20 | 36 |
| 2 | AIC R | 32 | 26 | 4 |
| AIC L | -36 | 20 | -2 |
| 3 | vlPFC R | 54 | 12 | 14 |
| vlPFC L | -50 | 8 | 4 |
| dlPFC/PMC R | 42 | 0 | 42 |
| dlPFC/PMC L | -34 | -4 | 40 |
| 4 | Temporo-parietal R | 62 | -34 | 34 |
| Temporo-parietal L | -58 | -32 | 32 |
| Parietal R | 30 | -48 | 40 |
| Parietal L | -30 | -48 | 38 |
| 5 | Occipital R | 46 | -58 | 12 |
| Occipital L | -46 | -70 | 8 |
| 6 | Basal Ganglia (BG) | strong activation with several local maxima throughout BG | | |
| Deactivations | | | | |
| Cluster | Area | MNI coordinates | | |
| X | Y | Z |
| 1 | Precuneus | 0 | -68 | 24 |
| PCC | 8 | -56 | 38 |
| 2 | Temporal Transverse L | -36 | -20 | 16 |
| Temporal Transverse R | 38 | -14 | 18 |
| 3 | Parietal R | 46 | -68 | 36 |

Table 2: MNI coordinates of the local maxima of all reported clusters

Discussion:

Based on the assumption that a common network mediating brain regulation exists, which can be identified by a meta analysis including rt-fMRI neurofeedback studies with a variety of target regions, we identified a regulation network that includes the anterior insula, basal ganglia, temporo-parietal area, the ACC, the dlPFC, the vlPFC and the visual association area including the temporo-occipital junction (see figure 2).



Figure 2: Schematic image 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), 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)

Anterior insula activation is known to occur during interoceptive cognition and self-awareness processes ([Craig, 2002](#_ENREF_8);[Critchley et al., 2004](#_ENREF_9)).

Similarly, basal ganglia are involved in as interoceptive processes ([Schneider et al., 2008](#_ENREF_32)) and also motivational ([Lehericy and Gerardin, 2002](#_ENREF_19);[Arsalidou et al., 2013](#_ENREF_2)) processing, as needed in feedback tasks. The temporo-parietal activation could possibly be caused by integration of the visual feedback and feedback related processes involving recall of memories ([Zimmer, 2008](#_ENREF_41)) as well as self-processing and multisensory integration of body-related information ([Arzy et al., 2006](#_ENREF_3)). PACC activation might reflect motivational aspects of the neurofeedback such as the rewarding effect of positive feedback and avoidance of negative feedback ([Amiez et al., 2005](#_ENREF_1);[Magno et al., 2006](#_ENREF_23);[Posner et al., 2007](#_ENREF_25)). The dlPFC and the premotor area are implicated in the imagination of action that is often part of the mental imagery used during neurofeedback ([Hanakawa et al., 2003](#_ENREF_14);[Lotze and Halsband, 2006](#_ENREF_22)). A similar involvement of the lateral PFC and the insula can be seen in experienced meditators during mindfulness meditation ([Farb et al., 2007](#_ENREF_11)) underlining the importance of these areas for self-awareness in the present. Finally, visual association area and the temporo-occipital junction activation may reflect visual imagery ([D'Esposito et al., 1997](#_ENREF_10);[Zimmer, 2008](#_ENREF_41)) as well as processing of the visual feedback.

In addition, the analysis showed some brain areas that are less active during neurofeedback. The PCC as well as the precuneus were less active during neurofeedback. This seems plausible, as these areas are part of the default mode network ([Raichle et al., 2001](#_ENREF_27);[Greicius et al., 2003](#_ENREF_12);[Raichle and Snyder, 2007](#_ENREF_28)) that is deactivated during cognitively demanding tasks.

Additionally, the transverse temporal area is deactivated, 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](#_ENREF_17)) and/or the task performance.

As most studies tried to upregulate 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](#_ENREF_13)) found that the dlPFC and vmPFC were simultaneously upregulated, suggesting that these areas might be involved in the regulation process. In accordance with this study, we found an upregulation of the dlPFC. Additionally, we detected pACC activation that is close to the vmPFC area. Due to our restricted field of view we have no data available to validate the vmPFC activation itself. Another study suggested that the anterior mid-cingulate cortex (region between the ACC and MCC that we called pACC) is involved in brain regulation ([Lee et al., 2012](#_ENREF_18)). This result is confirmed by our analysis as well. However, for the studies using a single ROI we cannot exclude the possibility that the shown effect was a results of the brain regulation (i.e., the activation was caused by the target region activation change) rather than the regulation process itself. Additionally, in all these studies, including this meta analysis, the regulation process will always be confounded by learning processes as the subjects learn to self-regulate by watching the feedback.

Interestingly, another study looking at sham neurofeedback reported very similar activations ([Ninaus et al., 2013](#_ENREF_24)). This confirms that independent of the outcome of the neurofeedback, a wide network of areas involved in cognitive control and sensory processing is recruited in attempted self-regulation.

Therefore, some studies already include a transfer run without feedback presentation. These transfer runs can help to disentangle learning effects from the actual regulation process. In the future, when more studies will be using a transfer run, we could thus set up a new retrospective analysis over studies including a contrast of transfer runs in comparison to normal feedback runs.

In addition, it should be noted that there 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). As soon as a gold standard is established, further analysis i.e., correlation of activation with regulation success would be desirable to validate this study.

Limitations:

Limitations include the limited field of view 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 addition, this analysis is retrospective and the design of the studies was not optimized for the meta analysis. Therefore, data acquisition parameters and paradigm (blocks, runs, sessions, up, down reg, stimuli, instructions) vary considerably across studies. However, the fact that our results show the regulation network consistently over variable studies indicates the general validity of these results.

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