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Meta-analysis of real-time fMRI neurofeedback studies: 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 underlying neuronal 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 overarching network involved in self-regulation. In an effort to detect regions that are responsible for the act of brain regulation itself, we performed a meta-analysis of data involving different target regions based on studies from different research groups.

We included twelve suitable studies that examined eight 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.

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 AIC has been implicated in interoceptive awareness of the body and cognitive control. BG 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, most importantly 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 AIC, 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.

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

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), the posterior cingulate cortex (Brewer and Garrison, 2014), the anterior insular cortex (AIC, Caria et al., 2007;Caria et al., 2010;Berman et al., 2013), posterior insular cortex (PIC, Rance et al., 2014), amygdala (Posse et al., 2003;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), 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, 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 efforts to control them (deCharms et al., 2005). If so, exactly which regions would be responsible for effects of self-regulation? Studies using a single region of interest suggest involvement of the dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC, Haller et al., 2010) and the anterior mid-cingulate cortex (Lee et al., 2012) to dorsal anterior cingulate cortex (Lawrence et al., 2013) in the regulation process per se. However, these studies did not explicitly explore the brain network responsible for feedback regulation. Indeed, 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 specifically 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 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. Our results suggest the existence of a self-regulation 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.ch) 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.

Twenty-eight studies were aggregate 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.

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	anterior Insula	14	1	4	DOWN	pain	4	30	functional

al. (2014)-AIC									
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

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 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 Figure 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 Figure 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

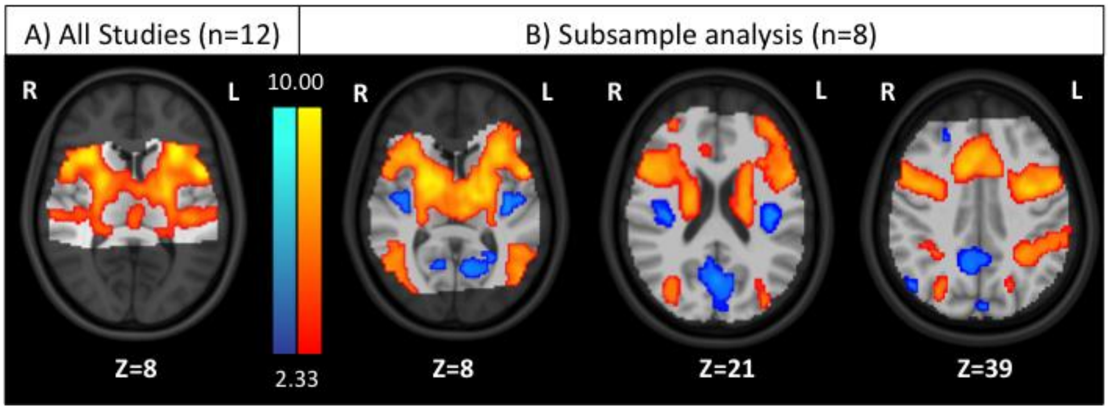

Figure 1: Main effect of the third level mixed effects analysis. (A) Results from the main analysis using all 12 studies with a restricted field of view (FoV) (B) Results from the subsample analysis of eight studies with a larger FoV. The light grey area indicates the overlapping FoV, areas in red-yellow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

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. 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.

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

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

Discussion

The 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 Figure 2).

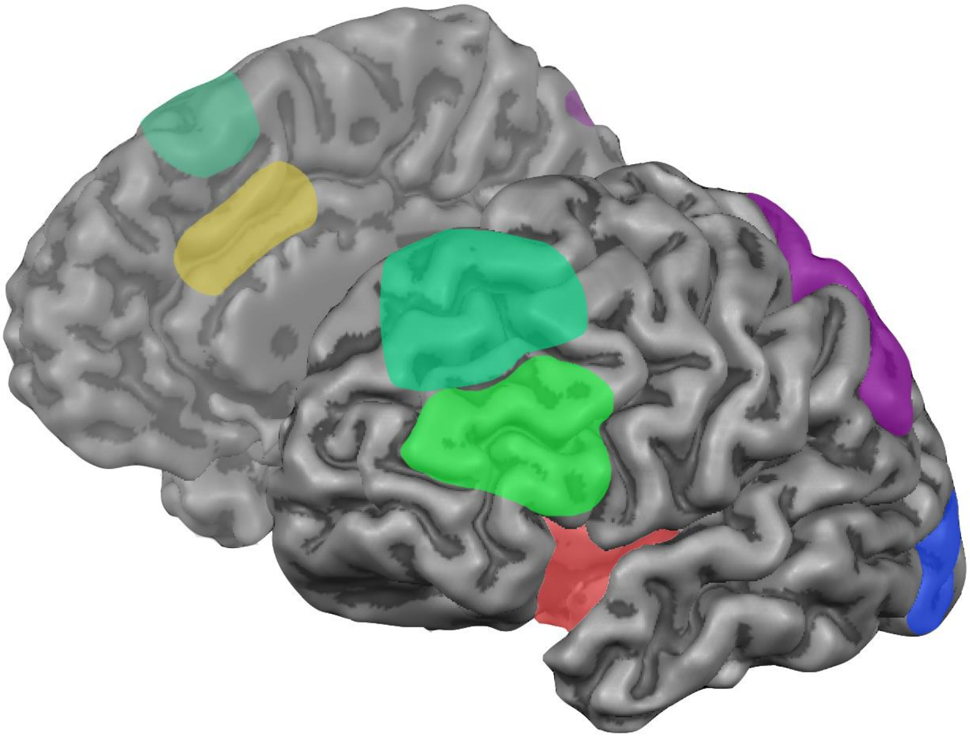

Figure 2: Schematic display of main brain areas involved in self-regulation. This network includes the ACC (yellow), the dorsolateral PFC extending to PMC (dark green), the ventrolateral PFC (light green), the anterior insula (red), part of the inferior and superior parietal lobule extending to the temporo-parietal 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;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 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.

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 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. Another study suggested that the anterior mid-cingulate cortex (region between the ACC and middle cingulate cortex (MCC) that we called pACC) is involved in brain regulation (Lee et al., 2012). 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 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 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 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.

Limitations

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). 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 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 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) due to the rather small number of suitable studies available in this field in general and the fact that this 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 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.

Conclusion

Brain regulation during rt-fMRI neurofeedback involves a complex regulation network, including notably AIC, BG, dlPFc, vlPFC, part of the temporo-parietal area and visual association areas including the temporo-occipital junction. Taking into account the limitation that the current investigation is a retrospective meta-analysis of rt-fMRI studies, which were not specifically designed for this purpose, our results suggest that some target regions of rt-fMRI 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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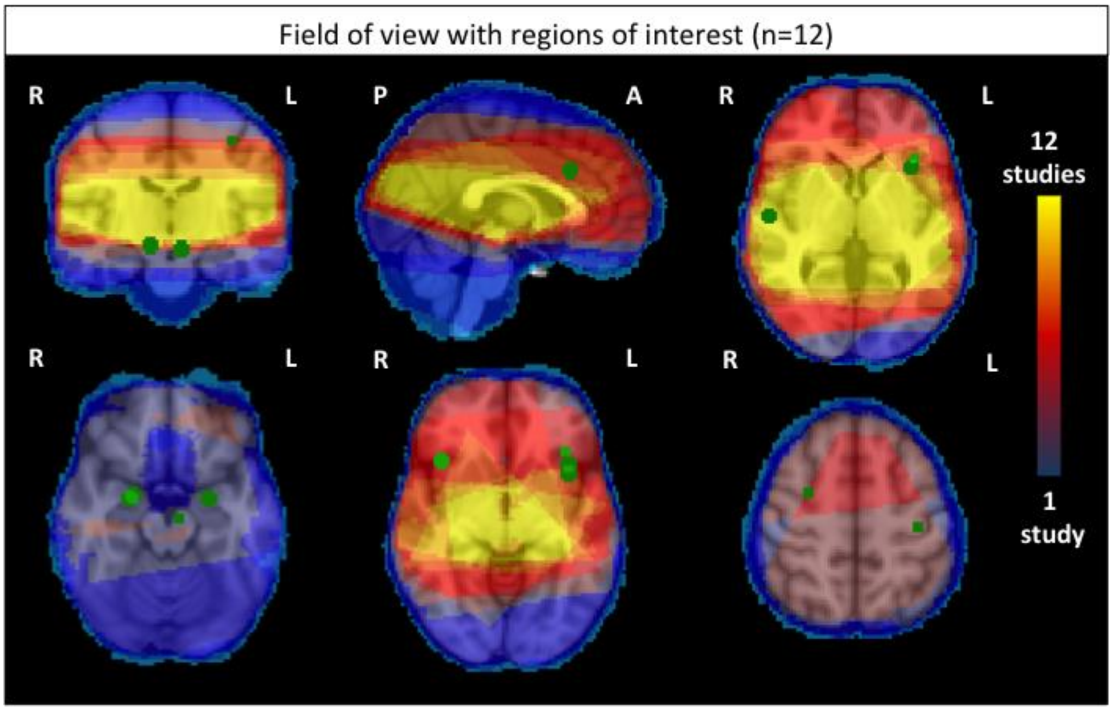
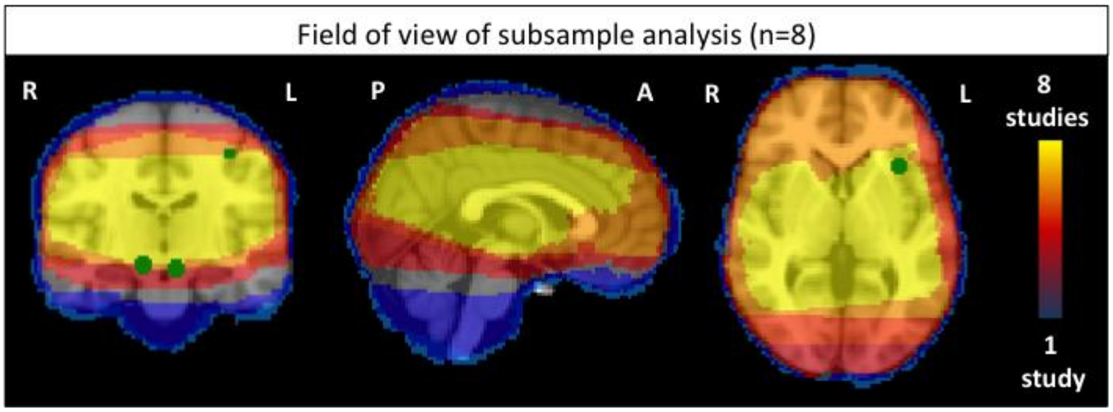
Supplementary Material

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.