SYSTEMATIC REVIEW OPEN

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Self-navigating the "Island of Reil": a systematic review of real-time fMRI neurofeedback training of insula activity

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Real-time fMRI (rtfMRI) neurofeedback (NF) is a novel noninvasive technique that permits individuals to voluntarily control brain activity. The crucial role of the insula in emotional and salience processing makes it one of the most commonly targeted regions in previous rtfMRI studies. To provide an overview of progress in the field, the present review identified 25 rtfMRI insula studies and systematically reviewed key characteristics and findings in these studies. We found that rtfMRI-based NF training is efficient for modulating insula activity and its associated behavioral/symptom-related and neural changes. Furthermore, we also observed a maintenance effect of self-regulation ability and sustained symptom improvement, which is of importance for clinical application. However, training success of insula regulation was not consistently paralleled by behavioral/symptom-related changes, suggesting a need for optimizing the NF training protocol enabling more robust training effects. Principles including inclusion of a well-designed control group/condition, statistical analyses and reporting results following common criteria and a priori determination of sample and effect sizes as well as pre-registration are also highly recommended. In summary, we believe our review will inspire and inform both basic research and therapeutic translation of rtfMRI NF training as an intervention in mental disorders particularly those with insula dysfunction.

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INTRODUCTION

The insula, known as the "Island of Reil", is located deep in the lateral sulcus [1] and extensively interconnected with other brain regions [1, 2]. Supported by an extensive network of connections, the insula represents an integrative hub in the emotion and salience network [3, 4] and plays a vital role in the integration of external-oriented sensory input and internal-oriented awareness [5, 6]. The insula is a cytoarchitectonically and functionally heterogenous region organized along a posterior-to-anterior gradient such that the anterior insula (AI) is mainly involved in interoceptive processing [7–9], emotion [10], risky decision-making [11] and empathy [12, 13], while the posterior insula (PI) primarily integrates somatosensory, vestibular, and motor information by receiving afferent projections from the spinal cord and brainstem via the thalamus [1]. Functional and structural dysregulations of the insular cortex are closely associated with various mental disorders, including anxiety disorder [14, 15], major depression disorder (MDD) [16–18], autism spectrum disorder [19–21], schizophrenia [22–24], addiction [25–27], alexithymia [28, 29] and Parkinson's disease [30, 31]. Thus, a noninvasive brain modulation approach that can directly target the insula and normalize its dysregulations may represent a novel and trans-diagnostically promising therapeutic strategy.

Real-time fMRI (rtfMRI) neurofeedback (NF) training capitalizes on recent progress in fMRI techniques and represents a noninvasive approach to modulate brain signals [32–35]. More specifically, rtfMRI NF can assist participants to gain voluntary control over brain activity by transforming the BOLD signal into real-time visual feedback. Previous studies have demonstrated that this approach allows individuals to gain self-regulation of most brain regions, including the amygdala [36, 37], the anterior cingulate cortex (ACC) [38, 39], the prefrontal cortex [40–42], the hippocampus [43], as well as the insula. The clinical application potential of rtfMRI NF training has also been supported by accumulating studies in clinical populations, including MDD [44, 45], anxiety disorder [46, 47], borderline personality disorder [48, 49], addiction [50, 51], post-traumatic stress disorder (PTSD) [52, 53], and attention deficit hyperactivity disorder [39, 54].

Based on the promising potential in both basic research and therapeutic application the rtfMRI NF field has progressed rapidly during the last decade. However, despite the promising translational potential of rtfMRI most therapeutic applications remain in the experimental stage. Thus, a systematic review of key characteristics of NF training and its associated behavioral and neural changes is important both for optimizing NF training protocol and facilitating the translation of rtfMRI into therapeutic application. Recent reviews focused on general progress in the field of rtfMRI (e.g. [32, 34, 55]), the therapeutic potential of rtfMRI NF training across different mental disorders (e.g. [56, 57]) or in specific disorders, such as eating disorders [58], schizophrenia [59],

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and addiction [60]. Although these reviews help us obtain a comprehensive understanding of progress in the field, very few reviews focus on the rtfMRI modulation of a specific target region. The two previous region-oriented reviews focused on the amygdala as a target region for emotion regulation [36] and therapeutic target in MDD [61] and suggest that a region-oriented systematic review can contribute to understanding characteristics of region-specific NF modulation and facilitating therapeutic translations in mental disorders characterized by region-specific dysregulation.

Given the crucial role of the insula in emotional and salience processing [4, 10], it has been one of the most popular regions that have been investigated in the field of rtfMRI [62]. Successful insula rtfMRI regulation has been repeatedly reported both in healthy and clinical populations (Table 1). Surprisingly, to date no study has systematically reviewed progress in the field of rtfMRI-based insula modulation. Against this background, we conducted a systematic review aiming to provide an overview of progress in this field, which may inspire researchers in optimizing NF training protocol design and thus facilitate therapeutic translations. More specifically, the main objectives of the present review are to provide a systematic overview addressing the following questions: (1) What characteristics/parameters (e.g., training protocol design, feedback types, regulation strategies, etc.) were used in rtfMRI NF training studies of insula regulation? (2) Can rtfMRI NF training consistently lead to successful voluntary control over the insula activity, and if so, can this training success be maintained to a "transfer" run without NF (i.e. the maintenance effect of self-regulation ability)? (3) What behavioral/symptom-related and neural changes can be induced by rtfMRI NF training of insula regulation?

METHODS

Literature search and inclusion criteria

A literature search was conducted by two authors independently following the PRISMA guidelines [63, 64] (Fig. S1). Specifically, literature on rtfMRI NF training on the insula was searched using the Web of Science, Science Direct and PubMed databases with the search terms "neurofeedback" and "fMRI" or "functional magnetic resonance imaging" or "functional MRI" and "insula" or "insular". A second search was then performed in these 3 databases with the following keywords: "rtfMRI" or "real time" or "real-time" and "fMRI" or "functional magnetic resonance imaging" or "functional MRI" and "insula" or "insular". Literature search was undertaken on April 2, 2024 and resulted in 865 articles (247 articles in PubMed, 138 articles in Science Direct and 480 articles in Web of Science). To avoid possible omission and mitigate potential publication bias [64, 65], we further searched on clinicaltrials.gov for possible trial registrations, comprehensive study protocol preregistrations, and registered reports and found 34 potential studies. The resulted 899 studies were further screened by analyzing titles and abstracts based on the following eligibility criteria: (1) written in English; (2) utilized rtfMRI-NF training (rather than other NF modalities such as electroencephalography, functional near-infrared spectroscopy or electrophysiology); (3) used BOLD signal as NF sources; (4) reported original research (i.e. reviews or commentaries were excluded). Based on these criteria, 40 articles were remained and entered into the next stage for full-text analyses, in which another 15 articles were excluded and resulted in 25 articles for the final analysis (details see Supplementary Materials).

Data extraction and publication bias

The following characteristics were extracted from each of the 25 qualified articles including (1) demographic information: population (healthy/clinical), sample size, age and gender distribution; (2) feedback characteristics: target regions and feedback types; (3) regulation strategies and directions; (4) localization approaches; (5) protocol design: number of training runs, number and duration of regulation blocks, practice and transfer run, control group/condition, and stimuli; (6) outcome measures and main findings. Training success was determined by comparing differences between the experimental and control groups, between regulation and rest blocks, or between the first and last runs. In addition, in line with inclusion criteria of recent rtfMRI meta-analysis studies [66, 67], 11 studies with available T or F values and degrees of freedom or other source data (e.g., mean values, standard deviation) were selected for conducting a quantitative effect size assessment of training success using the comprehensive meta-analysis software [68]. Training success in this exploratory analysis was defined by the difference in insula activity between the first and the last training runs in the NF training group, which led to the most qualified studies (see *NF training success on insula regulation*). An exploratory publication bias assessment was also conducted based on these 11 studies using the Egger's test and showed a significant publication bias ($t = 5.79$, $p < 0.001$; Figure S3). Furthermore, we conducted a quality assessment based on the Consensus on the Reporting and Experimental Design of Clinical and Cognitive-Behavioural FMRI-neurofeedback Studies (CRED-NF checklist; [69]) and showed a moderate quality of qualified studies included in the present study with an averaged consistency about 0.61 (see Supplementary Table 1).

RESULTS

Participants

The final 25 qualified articles consisted of 14 studies in healthy and 11 in clinical populations (Table 1 and Fig. 1A). Clinical studies included individuals with schizophrenia [70], disruptive behavior disorder (DBD) [71], obsessive-compulsive disorder (OCD) [72], spider phobia [47], MDD [73, 74], alcohol and tobacco addiction [75–78], and criminal psychopaths [79]. Significant training effects on insula regulation were found in 13 of 14 studies (92.86%) in healthy subjects and 8 of 11 studies in clinical populations (72.72%) (Fig. S2). Of note the 2 clinical studies showing no significant training effects were conducted in comparably small samples and in patient groups characterized by marked regulatory control deficits, i.e. OCD patients ($n = 3$; [72]) and criminal psychopaths ($n = 4$; [79]).

There were 599 participants in total and sample size ranged from 3 to 84, with only 6 studies more than 30 (Fig. 1B). For 22 studies information on gender was available and the percentage of females was 45.74% with 20 studies including both genders while 2 studies only recruited male [80] or female participants [47]. The remaining 3 studies did not report gender information [75, 78, 79]. For age, 3 studies only reported age range and one study did not report specific age information [75, 78, 81, 82]. The mean age of the remaining 21 studies is 28.81 years old. While the youngest sample (mean = 11.6) was observed in a study examining the rtfMRI training effects on the emotion regulation network in adolescents [83], the most senior sample (mean = 48.44) was found in a clinical study on patients with MDD [73]. Detailed demographics are presented in Table 1 and Fig. 1.

Feedback types and target regions

RtfMRI NF is normally delivered in a visual form (e.g., a thermometer bar or magnitude of monetary reward) intermittently or continuously (e.g. [78, 82, 84]). All included studies displayed feedback based on regional-specific BOLD signal amplitude of the insula, which included 7 studies focusing on the right AI, 6 studies focusing on the left AI, 5 studies focusing on bilateral AI, one study focusing on the left PI, and 6 studies focusing on the whole insula (Table 1 and Fig. 1C). With respect to the feedback type, 21 studies employed continuous feedback,

Table 1. Participants' demographics, feedback and regulation strategies.

Study	Population	N (F)	Age M (SD)	Target ROIs	Feedback types	Regulation direction	Regulation strategies in regulation (rest)
Berman et al. [84]	Healthy	14 (8)	29.7 (8.2)	rAI	Continuous	Up	Mental imagery (Relaxation)
Böttinger et al. [71]	DBD and healthy	25 (5)	14.57 (1.64)	Insula/amygdala	Continuous	Up	Free (Free)
Buyukturkoglu et al. [72]	OCD	3 (2)	23.33 (3.09)	bAI	Intermittent	Down	Free (Free)
Caria et al. [85]	Healthy	15 (9)	25.13[a]	rAI	Continuous	Up	Mental imagery (Number counting)
Caria et al. [86]	Healthy	27 (15)	27.51[a]	lAI	Continuous	Up	Mental imagery[a]
Emmert et al. [91]	Healthy	28 (14)	27.5 (2.3)	lAI[b]	Continuous	Down	Free (Free)
Frank et al. [80]	Healthy (obese/lean)	21 (0)	26.24 (0.86)	bAI	Continuous	Up	Mental imagery (Number counting)
Johnston et al. [81]	Healthy	13 (9)	21–52	Insula/amygdala/VLPFC	Continuous	Up	Mental imagery[a]
Kadosh et al. [83]	Healthy	17 (8)	11.6 (2.5)	rAI	Continuous	Up/Down	Mental imagery (Relaxation)
Kanel et al. [88]	Healthy	20 (13)	24.6 (3.32)	rAI	Continuous	Up	Emotional voice empathizing (Number counting)
Karch et al. [75]	Alcohol addiction and healthy	27[a]	18–60	Insula/ACC/DLPFC	Continuous	Down	Free (Free)
Karch et al. [76]	Tobacco addiction (abstinence/relapse)	36 (11)	43.83 (12.37)	Insula/ACC/DLPFC	Continuous	Down	Free (Free)
Karch et al. [77]	Alcohol addiction (abstinence/relapse)	48 (7)	45.5 (11.52)	Insula/ACC/DLPFC	Continuous	Down	Free (Free)
Lawrence et al. [87]	Healthy	24 (12)	27.33 (4.71)	rAI	Continuous	Up	Mental imagery/Body awareness (Number counting)
Linden et al. [73]	MDD	16 (3)	48.44 (12.99)	Insula/DLPFC	Continuous	Up	Mental imagery (Relaxation)
Mehler et al. [74]	MDD	32 (21)	47.07 (12.42)	Insula	Continuous	Up	Free (Number counting)
Popovova et al. [90]	Healthy	56 (27)	23.84 (3.3)	rAI	Intermittent	Up	Free (Number counting)
Rana et al. [78]	Nicotine addiction	4[a]	-	bAI	Intermittent	Down	Free[a]
Rance et al. [93]	Healthy	10 (4)	29 (6.48)	lPI[b]	Continuous	Up/Down	Free (Mental arithmetic)
Ruiz et al. [70]	Schizophrenia	9 (5)	26.3 (4.5)	bAI	Continuous	Up	Mental imagery (Relaxation)
Sitaram et al. [79]	Criminal with psychopaths	4[a]	31.5 (3.5)	lAI	Continuous	Up	Mental imagery (Number counting)
Veit et al. [92]	Healthy	11 (8)	21–28	lAI	Continuous	Up/Down	Mental imagery (Passively watching)
Yao et al. [82]	Healthy	37 (18)	21.97 (1.4)	lAI	Continuous	Up	Mental imagery (Relaxation)
Zhang et al. [89]	Healthy	84 (41)	21.55 (2.06)	lAI	Continuous	Up	Heartbeat interoception (Relaxation)
Zilverstand et al. [47]	Spider phobia	18 (18)	21.2 (1.78)	rAI	Intermittent	Down	Cognitive reappraisal (Relaxation)

ACC anterior cingulate cortex, *AI* anterior insula, *b* bilateral, *DBD* disruptive behavior disorder, *DLPFC* dorsolateral prefrontal cortex, *F* female's number, *l* left, *M* mean, *MDD* major depressive disorder, *N* numbers of subjects, *OCD* obsessive-compulsive disorder, *PI* posterior insula, *r* right, *SD* standard deviation, *VLPFC* ventrolateral prefrontal cortex.

[a]No reported results in articles.

[b]Two training groups with different target ROIs.

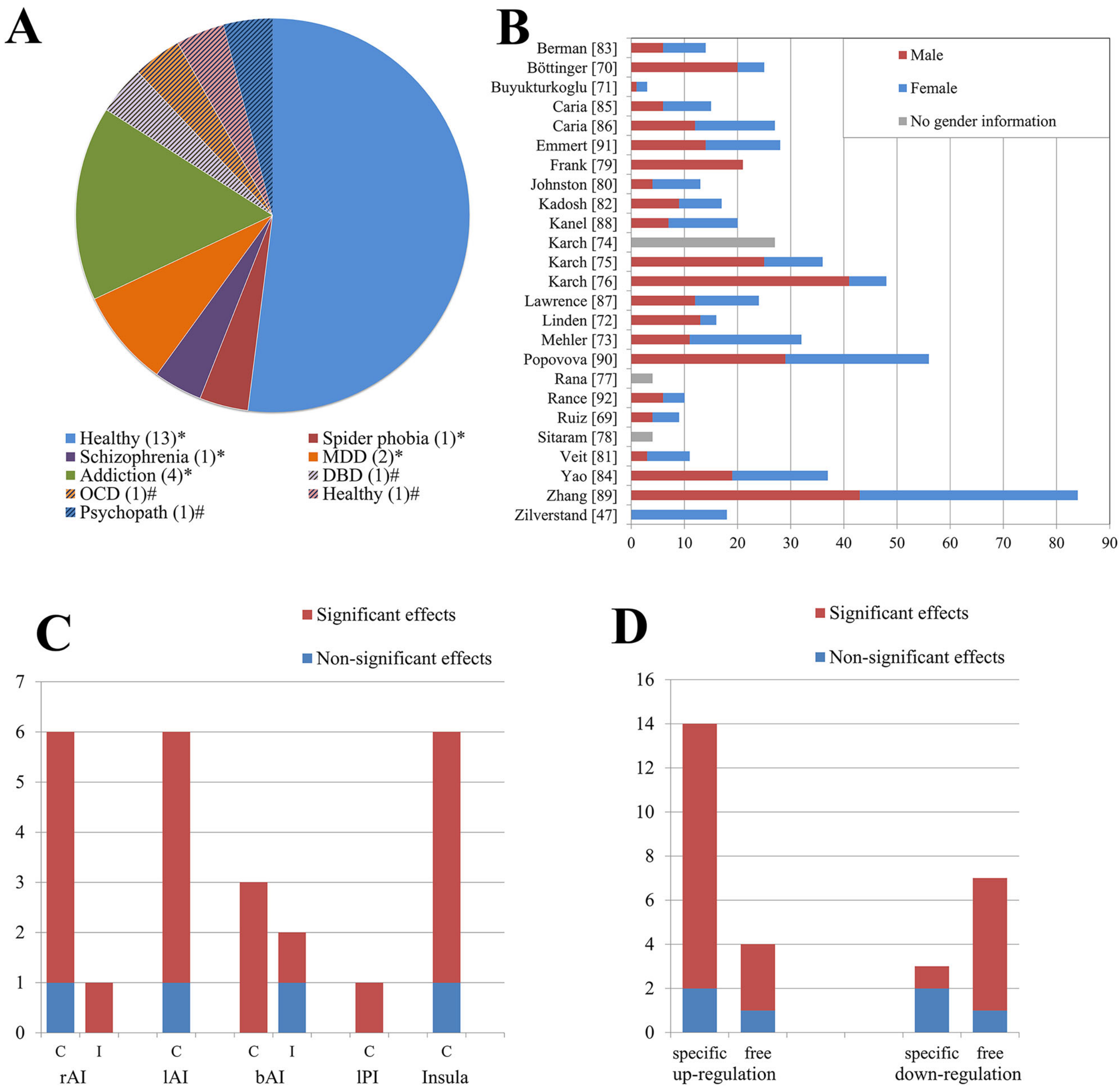

Fig. 1 Demographic information, neurofeedback types and regulation directions. Population (**A**) and gender distribution (**B**) in the qualified 25 studies. (**C**) Feedback types categorized by target regions. (**D**) Types of regulation strategies categorized by regulation directions. AI anterior insula, b bilateral, C continuous feedback, I intermittent feedback, Insula-dmFC functional connectivity between the insula and dorsomedial frontal cortex, l left, PI posterior insula, r right, * Studies showing significant effects on insula regulation; # Nonsignificant training effects on insula regulation.

which was continuously presented to participants in regulation/rest blocks. The remaining 4 studies used intermittent feedback presented as the mean activity of a whole block at the end of each regulation/rest block (Table 1). Significant training effects were found in 3 of 4 studies (75%) using intermittent feedback and 18 of 21 studies (85.71%) using continuous feedback (Fig. S2).

Regulation strategies and direction

Efficient NF training commonly depends on valid regulation strategies which can be specific following of instructions or freely developed by participants themselves (i.e. free strategies). While 10 studies used free strategies, 15 studies provided specific strategies with mental imagery being the most popular strategy (12 studies) (Table 1 and Fig. S2). Significant training effects were observed in 8 of 10 studies (80%) using free strategies and in 13 of 15 studies (86.67%) using specific strategies (Fig. S2). To bring brain activation back to baseline level, participants were asked to close their eyes and rest, relax, focus on a cross, count numbers, or view neutral stimuli during rest blocks (Table 1).

With respect to regulation direction, there were 15 studies on up-regulation, 7 studies on down-regulation, and 3 studies on both up- and down-regulation (Table 1 and Fig. S2). Twelve of the 15 (80%) up-regulation studies [70, 73, 74, 80–82, 85–90] and 6 of 7 (85.71%) down-regulation studies [47, 75–78, 91] reported successful regulation of insula activity. For the 3 studies involving both up- and down-regulation, all of them reported successful up-regulation [83, 92, 93] and one of them reported successful down-regulation [93] of the insula activity. Thus, in total there were 15 studies reporting training success (83.33%) among the 18 studies involving up-regulation and 7 studies reporting training success (70%) among the 10 studies involving down-regulation (Fig. 1D). In contrast to 4 out of 18 up-regulation studies applying free regulation strategies, most of the down-regulation studies used free regulation strategies (7 in 10 studies) (details see Table 1 and Fig. 1D).

Localizing approaches

Precise localization of the target region is vital for obtaining desired feedback. In the present study, there were 8 studies employing anatomical localization, 14 studies applying functional localization, and 3 studies combining both approaches to define the insula (Table 2 and Fig. S2). We categorized functional localization tasks into 3 main types, including emotional recall tasks, passive observation tasks (emotional/substance-related pictures) and other specific tasks (see Table 2). While all of the 8 studies using anatomical localization showed significant training effects, 13 of the 14 studies (92.86%) applying functional localization reported significant training effects. The remaining 3 studies using both approaches reported no significant training effects (Fig. S2). Note that 2 of the 3 studies showing no significant training effects were the same as the 2 studies with low sample sizes in OCD patients ($n = 3$) and criminal psychopaths ($n = 4$) as discussed in the "Participants" section [72, 79].

Protocol design

Training runs. Training protocols in the 25 qualified studies employed between 3 and 24 training runs (mean = 8.92), with 12 studies incorporating 3 or 4 runs performed on a single day and 13 studies (including 9 clinical studies) comprising 6 or more runs separated into 2–10 days (Table 2). Clinical studies included more training runs separated on different days than healthy subject studies (11.73 vs. 6.71 runs respectively). Each run included 4–12 regulation blocks (mean = 6.2) alternating with rest blocks with a single regulation block ranging from 9–45 s (mean = 28.64). Given the hemodynamic nature of the BOLD signal, the duration of each block in most of the studies (23 studies) ranged from 20–45 s and only 2 studies had shorter blocks of 9 s and 12.5 s respectively [47, 92].

Practice and transfer runs. While a practice run is set to help participants familiarize the training procedure before formal NF training, a transfer run is applied to examine the maintenance of training effects without feedback. In the 25 studies, only 4 included a practice run [47, 84, 90, 93] and 3 of them reported training success [47, 90, 93]. Eleven studies included transfer runs (Table 2) and 9 of them tested maintenance effects in a transfer run immediately following NF training (Table 2). More specifically, 3 studies reported significant maintenance effects in transfer runs immediately [88, 89] or 2 days following NF training [82]. The last study also reported that changes in rsFC of the AI but not in the behavioral performance induced by NF training were also maintained in the transfer run [82].

Control group/condition. Inclusion of a control group/condition can exclude the possibility that the NF training effect is not specific to NF. In the 25 qualified studies, 13 studies included a control group in which 8 studies used sham feedback from an unspecific or task-irrelevant region [74–77, 82, 87–89], followed by 2 studies with no feedback [47, 73] and 3 studies using 2 control groups with sham or no feedback [85, 86, 90]. Sham control regions included a whole top slice far from the insula [82, 85, 86, 88, 89], the primary visual cortex [90], the parahippocampal place area [74], the cuneus [75], the parietal cortex [76, 87], the occipital cortex [77], and the middle temporal gyrus [89]. Among the other 12 studies without a control group, there were 2 studies comprising 2 NF training groups comparing training differences between two different target ROIs (AI vs. ACC [91]) or ability in self-regulation of the insula between lean and obese individuals [80]. In addition to sham control groups, the bidirectional regulation (up- and down-regulation) in a within-group design was applied as a control condition in 3 studies [83, 92, 93].

Stimuli. In the 25 qualified studies, 21 studies presented stimuli to participants and 4 studies did not use any stimuli [80, 84, 85, 90]. More specifically, 18 studies presented participants with different visual stimuli, including emotional faces [70, 83], emotional/threat-related stimuli [73, 74, 79, 81, 86, 87, 92], affective video clips [71], pain empathy-evoking pictures [82, 89], symptom-related aversive scenes [47, 72], and substance-related pictures [75–78]. Among these 18 studies, 13 of them presented visual stimuli from the International Affective Picture System (IAPS) [72–77, 79, 81, 82, 86, 87, 89, 92], one study displayed video stimuli from the Emotional Movie Database [71], 2 studies used stimuli from the NimStim Face Stimulus Set [70, 83], one study used custom-designed stimuli [47], and one study did not report the source of stimuli used [78], although some of them additionally used custom-designed stimuli or stimuli from the Internet [72, 75–77]. The remaining 3 studies used stimuli of other modalities, with 2 studies using painful heat stimulation to induce the insula activity during regulation [91, 93] and one study presenting emotional auditory stimuli to aid participants in implementing regulation strategies [88]. Details of specific stimulus sources used and presentation time points (e.g., during the localizer or NF training task) are presented in Table 2. Furthermore, while there were 9 studies in the 10 down-regulation studies presenting stimuli during regulation/rest blocks, only 4 in 18 up-regulation studies did the same.

Outcome measurements

NF training success on insula regulation. Training success of insula regulation was mainly determined by comparing the difference in insula activity between the NF training and control groups, between the first and the last training runs, or between regulation and rest blocks. Successful insula regulation was reported in 21 of the 25 qualified studies (84%) based on these different comparison approaches. The most consistent training success was determined by a significant difference in insula activity between the first and the last training runs in the NF training group, which was found in 15 studies (10 studies in healthy populations; .). Seven of the studies (some studies reported training success based on more than one comparison) reported significant differences between the regulation and rest blocks in the NF training group and 3 studies reported significant differences between the NF training and control groups (details see Table 3). A further meta-analysis of 11 studies with available statistics showed a medium effect size of NF training based on the comparison between the first and the last training runs in the NF group (SMD = 0.633, 95%CI = 0.370–0.896, Z = 4.721, $p < 0.0001$; Fig. 2).

Behavioral outcomes associated with training success. Behavioral effects associated with NF training were measured in 22 studies using different types of behavioral/symptom-related questionnaires/ratings/tasks (Table 4). Similar to measurement of training success, significant behavioral effects were also determined by these 3 comparison approaches. Significant behavioral effects were found in 6 studies in healthy and 7 studies in clinical populations. In the 6 healthy population studies, while one study of AI up-regulation showed significantly higher pain empathy ratings in the NF compared with the control groups [82], the other 3 studies reported increased valence ratings to aversive pictures in the last compared with the first training run [86] and increased reaction time, suggestive of improved alertness in the post-training relative to pre-training measurement in a cognitive attention task [90] during up-regulation, but decreased pain

Table 2. Characteristics of neurofeedback training protocol design.

Study	Feedback in control groups	Practice run	Transfer run	Training runs		Stimuli (Ratings)	Visual stimuli dataset	Time point of stimuli delivery	Localizer	Localizer tasks
				Run×Visit	Blocks (Duration)					
Berman et al. [84]	/	Yes	Yes	4	5 (30)	/	/	/	both	Suppression task vs. rest
Böttinger et al. [71]	/	/	Yes	10×2	7 (40)	Affective videos (No)	EMD	Training[b]	both	Implicit emotion vs. target match
Buyukturkoglu et al. [72]	/	/	Yes	4×4	6 (27)	Disgusting pictures (Yes)	IAPS&CD/CD/CD	Loc/Training[b]/Pre/Post	both	Disgust vs. neutral pictures
Caria et al. [85]	Sham/No feedback	/	Yes	4	4 (22.5)	/	/	/	anatomical	/
Caria et al. [86]	Sham/No feedback	/	/	4	5 (30)	Aversive pictures (Yes)	IAPS	Training	anatomical	/
Emmert et al. [91]	/	/	/	4	4 (30)	Heat pain (Yes)	/	Loc/Training[b]	functional	Pain stimulation vs. rest
Frank et al. [80]	/	/	/	3×2	7 (30)	/	/	/	anatomical	/
Johnston et al. [81]	/	/	/	3	12 (20)	Emotional pictures (No)	IAPS	Loc	functional	Negative vs. neutral pictures
Kadosh et al. [83]	/	/	/	4	9 (20)	Face pictures (No)	NimStim	Loc	functional	Emotional go/no-go
Kanel et al. [88]	Sham feedback	/	Yes	10 + 6	8 (24)	Emotional voice (No)	/	Training[b]	anatomical	/
Karch et al. [75]	Sham feedback	/	/	4	4 (40)	Alcohol pictures (No)	IAPS&CD/IAPS&CD	Loc/Training[b]	functional	Alcoholic vs. neutral pictures
Karch et al. [76]	Sham feedback	/	/	3×3	4 (40)	Tobacco pictures (No)	IAPS&CD/IAPS&CD	Loc/Training[b]	functional	Tobacco vs. neutral pictures
Karch et al. [77]	Sham feedback	/	/	3×3	4 (40)	Alcohol pictures (No)	IAPS&CD/IAPS&CD	Loc/Training[b]	functional	Alcoholic vs. neutral pictures
Lawrence et al. [87]	Sham feedback	/	/	4	5 (30)	Affective pictures (Yes)	IAPS	Pre/Post	anatomical	/
Linden et al. [73]	No feedback	/	/	3×4	12 (20)	Emotional pictures (No)	IAPS	Loc	functional	Emotional pictures vs. rest
Mehler et al. [74]	Sham feedback	/	Yes[a]	6×4	4 (20)	Emotional pictures (No)	IAPS	Loc	functional	Positive vs. neutral pictures
Popovova et al. [90]	Sham/No feedback	Yes	Yes	5×2	5 (40)	/	/	/	anatomical	/
Rana et al. [78]	/	/	Yes	4×2	6 (26)	Nicotine pictures (No)	NR	Training[b]/Pre/Post	anatomical	/
Rance et al. [93]	/	Yes	/	6×4	6 (45)	Heat pain (Yes)	/	Training[b]	anatomical	/
Ruiz et al. [70]	/	/	Yes	3×4	6 (30)	Face pictures (Yes)	NimStim	Post	functional	Emotional recall vs. rest

Table 2. continued

Study	Feedback in control groups	Practice run	Transfer run	Training runs		Stimuli (Ratings)	Visual stimuli dataset	Time point of stimuli delivery	Localizer	Localizer tasks
				Run×Visit	Blocks (Duration)					
Sitaram et al. [79]	/	/	/	4×3	6 (30)	Aversive pictures (Yes)	IAPS	Pre/Post	functional	Emotional recall vs. count number
Veit et al. [92]	/	/	/	3	12 (9)	Aversive pictures (No)	IAPS/IAPS	Loc/Training[b]	functional	Aversive vs. neutral pictures
Yao et al. [82]	Sham feedback	/	Yes[a]	4	5 (30)	Painful pictures (Yes)	IAPS&EPSS/EPSS	Loc/Training	functional	Painful vs. non-painful pictures
Zhang et al. [89]	Sham feedback	/	Yes	4	5 (30)	Painful pictures (Yes)	IAPS&EPSS	Loc/Pre/Post	functional	Painful vs. non-painful pictures
Zilverstand et al. [47]	No feedback	Yes	/	3	4 (12.5)	Spider pictures (Yes)	CD/CD	Loc/Training[b]	functional	Spider pictures vs. rest

The information in the "Time point of stimuli delivery" column corresponds sequentially to the information in the "Visual stimuli dataset" column.
EMD emotional movie database, *EPSS* empathy for pain stimuli system, *IAPS* international affective picture system, *Loc* stimuli were used in functional localization task, *NimStim* nimstim face stimulus set, *NR* not report, *Pre/Post* stimuli were presented in the pre-training or post-training tasks, *CD* visual stimuli were custom-designed or from the internet.
[a]Transfer runs were performed 2 days [82] or 2 weeks [74] after NF training.
[b]Stimuli were only presented during regulation blocks in the NF training task.

perception ratings to heat stimulation in the last training run relative to the functional localizer task during down-regulation [91]. In the remaining 2 studies, they showed NF training affected participants' subjective perception of regulation strategy implementation or training success such that one study of AI up-regulation reported increased rating scores for degrees of regulation strategy implementation in the NF training compared with the control groups [89] and the other one of AI bidirectional regulation showed significantly increased ratings of perceived training success over runs within the NF group [92].

In 2 clinical studies on up-regulation, NF training induced symptom relief in depression as measured by mood and symptom severity questionnaires post-training relative to pre-training [73] and improvement in recognition accuracy to disgust faces but impaired recognition accuracy to happy faces in schizophrenia patients in the regulation compared with the rest blocks [70]. In the remaining 5 clinical studies on down-regulation, while 2 studies showed improvement in anger control and impulsiveness of patients with alcohol dependence [77] or lower anxiety levels to spider pictures in individuals with spider phobia [47] in the NF training relative to the control groups, the other 3 studies reported decreased disgust levels to symptom-evoking stimuli in OCD [72], improvement in depression symptoms in depression patients in the post- relative to pre-training tests [74], or decreased craving scores in addicted smokers [78]. All details of behavioral outcome measurements are shown in Table 4.

Seven studies included follow-up measurements varying from 2 days to 6 months after NF training [47, 72, 74, 77, 78, 82, 90], with one study in healthy participants showing a sustained improvement in alertness, as measured by a cognitive attention task [90], and 3 clinical studies reporting a sustained decrease in disgust ratings to symptom-evoking stimuli in OCD [72], craving scores in addicted smokers [78], or symptom levels in individuals with spider phobia [47] (Table 4).

Neural outcomes associated with training success. Neural outcomes associated with training success were measured by changes in functional connectivity during NF training or resting-state recording. Nine studies examined functional connectivity changes during NF training and only found increased functional connectivity of the insula mainly with frontal regions and additionally with the cingulate cortex and amygdala (Table 3). Another study, in which only one out of 4 subjects finished all of the training runs, showed causal functional connectivity changes mainly driven by the posterior cingulate cortex (Table 3) and thus findings in this respect should be interpreted with caution given the small sample size [79].

For rsFC changes, 5 studies recorded resting-state data pre- and post-training [75–78, 82] and 2 studies reported significant rsFC changes, with one study in healthy subjects reporting increased rsFC of the insula mainly with regions of the empathic network/mirror neuron system (MNS) but decreased rsFC with regions of the default mode network [82] and the other one in patients with alcohol use disorder showing increased rsFC of the insula mainly with frontal regions [75].

Brain-behavior associations. Brain-behavior associations were reported in 10 studies. Five studies in healthy subjects demonstrated significant associations between NF-induced changes of the insula activity and different behavioral measurements including changes in valence ratings to aversive pictures [86], pain empathy ratings [82], unpleasantness ratings to painful heat stimulation [93], interoceptive accuracy measured following NF training [89], and dispositional empathy levels as measured by the Interpersonal Reactivity Index [88]. In another 4 clinical studies, NF-induced insula activity was found to be significantly correlated with improvement in recognition accuracy of disgust faces [70], rule-breaking behavior as measured by the Child Behavior

Table 3. Statistics of training success contrasts on insula self-regulation and associated functional connectivity changes.

Study	Up/Down	EG vs. CG		First vs. Transfer	First vs. Last		Regulate vs. Rest		Functional connectivity	
		Across runs	Transfer	EG	EG	CG	EG	CG	Region	Findings
Berman et al. [84]	Up	/	/	NS	NS	/	/	/	dmPFC	↑ $p < 0.0001$
Böttinger et al. [71]	Up	/	/	/	NS	/	/	/	/	/
Buyukturkoglu et al. [72]	Down	/	/	NS	NS	/	-	/	/	/
Caria et al. [85]	Up	-	-	NS	$p < 0.012$	NS	/	/	/	/
Caria et al. [86]	Up	NS	/	/	$p = 0.012$[a]	MI ($p = 0.034$)	/	/	/	/
Emmert et al. [91]	Down	/	/	/	$p < 0.05$	/	/	/	vlPFC	↑ $p < 0.05$
Frank et al. [80]	Up	/	/	/	$p < 0.05$	/	/	/	MCC/MTC	↑ $p < 0.001$
Johnston et al. [81]	Up	/	/	/	$p < 0.029$	/	$p = 0.002$	/	/	/
Kadosh et al. [83]	Up/Down	/	/	/	NS	/	$p = 0.023$	/	Amygdala[b]	$p = 0.001$[c]
Kanel et al. [88]	Up	NS	$p = 0.018$	NS	$p = 0.041$	NS	/	/	/	/
Karch et al. [75]	Down	/	/	/	$p = 0.048$	NS	/	/	mPFC/dlPFC	↑ $p < 0.05$
Karch et al. [76]	Down	/	/	/	/	/	$p < 0.05$	/	/	/
Karch et al. [77]	Down	NS	/	/	/	/	/	/	/	/
Lawrence et al. [87]	Up	-	/	/	$p = 0.03$[a]	NS	/	/	/	/
Linden et al. [73]	Up	/	/	/	$p = 0.04$	/	/	/	/	/
Mehler et al. [74]	Up	NS	NS	$p = 0.023$	-	-	$p < 0.05$	/	/	/
Popovova et al. [90]	Up	NS	NS	$p = 0.0008$	$p = 0.005$	$p = 0.013$	/	/	/	/
Rana et al. [78]	Down	/	/	-	$p < 0.05$	/	/	/	/	/
Rance et al. [93]	Up/Down	/	/	/	$p < 0.05$	/	$p < 0.05$	/	/	/
Ruiz et al. [70]	Up	/	/	NS	$p = 0.02$	/	/	/	mPFC/Amygdala[b]	$p < 0.01$
Sitaram et al. [79]	Up	/	/	/	NS	/	/	/	PCC[b]	$p < 0.05$
Veit et al. [92]	Up/Down	/	/	/	NS	/	$p < 0.001$	/	dmPFC/vlPFC	↑ $p < 0.001$ [c]
Yao et al. [82]	Up	$p = 0.041$	$p = 0.006$	/	$p = 0.011$	NS	/	/	dlPFC/dmPFC/IPL	↑ $p < 0.001$
Zhang et al. [89]	Up	$p = 0.018$	$p = 0.031$	/	NS	/	/	/	vmPFC/ACC/aPFC	↑$p < 0.005$
Zilverstand et al. [47]	Down	$p < 0.05$	/	/	$p < 0.05$	NS	$p < 0.05$	NS	/	/

CG control group receiving sham feedback from unrelated region, *EG* experimental group receiving real feedback from the insula, *MI* the control group used emotional imagery without feedback, *NS* not significant, *Transfer* no feedback.
-Did not report.
[a]Significant interaction effects.
[b]Granger Causality Modeling.
[c]Significant effects of functional connectivity was found in up-regulation.

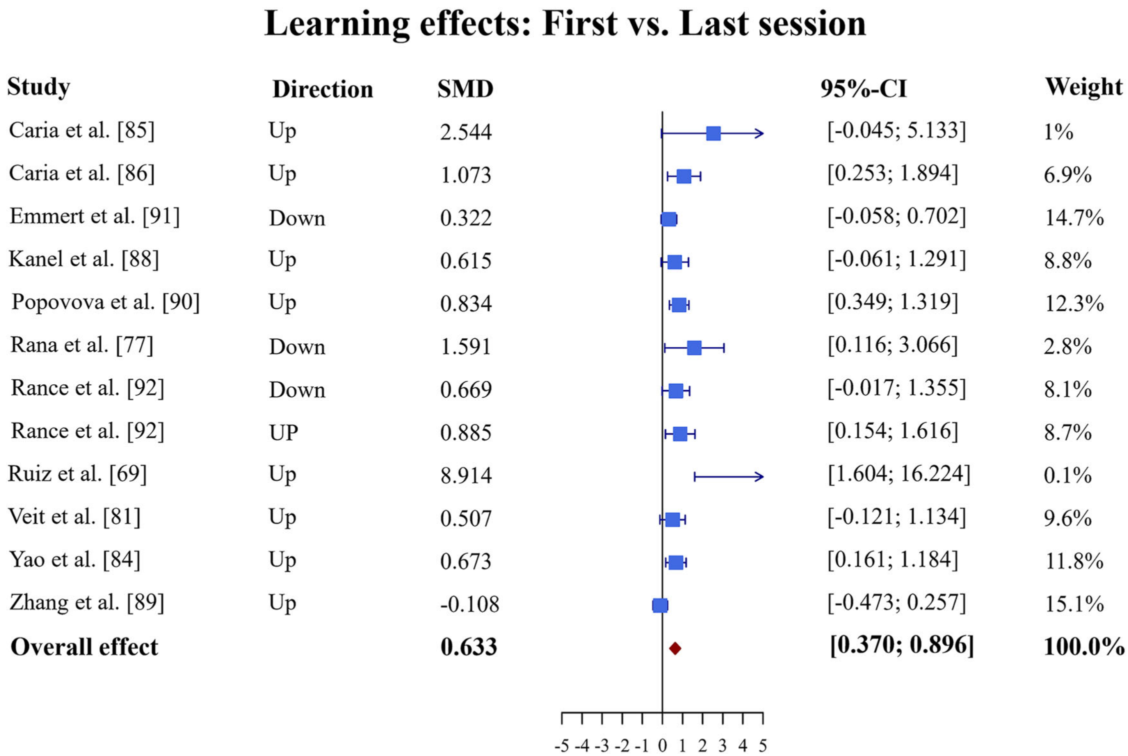

Fig. 2 Forest plots showing the difference in Neuromodulation (i.e. regulation vs. rest) between the first (or practice) and last NF runs within the NF training group.

Checklist [71], fear/belief of spiders as measured by the Fear of Spider Questionnaire and Spider Belief Questionnaire [47], and depressive symptom severity as measured by the Hamilton Rating Scale for Depression and mood as measured by the Positive and Negative Affect Schedule [73] (Table 4). The last study did not find any significant correlations [90].

DISCUSSION

In the present systematic review, we obtained 25 qualified studies on insula regulation based on rtfMRI NF training. Participants' demographics, feedback types, regulation strategies and direction, localizing approaches, protocol design, outcome measurements and main findings were systematically reviewed to provide a comprehensive overview of progress in the field of rtfMRI NF training of insula regulation.

In the 25 qualified studies, rtfMRI NF training of insula regulation has been applied in both healthy individuals and clinical populations with schizophrenia, DBD, OCD, spider phobia, MDD, addiction, and criminal psychopaths. In healthy individuals (14 studies), NF training of insula regulation was applied to modulate their behavioral responses in the domain of emotional (valence), attentional, empathic, and pain processing that are closely associated with the insula function [82, 86, 90, 91]. Similarly in clinical studies (11 studies), NF training was applied to normalize altered emotional/cognitive responses or to improve symptom severity in disorders characterized by insula dysfunction [1, 94]. Based on different comparison approaches, 21 of the 25 qualified studies (84%) reported successful self-regulation of the insula, with 13 of 14 studies in healthy (92.86%) and 8 of 11 studies in clinical populations (72.73%). The average age of participants varied from 11.6–48.44 years including both males and females (Table 1). Training success as measured by comparison between the first and the last training runs in the NF group reflecting improvement of self-regulation ability with progress over training runs was the most consistently reported method (15 of the 21 studies). A further meta-analysis showed a medium effect size of training success based on this comparison in 11 studies with available statistics. Comparable training efficacy has been reported in recent review/meta-analysis studies on different target regions [56, 67]. Although the training success rate may be inflated by publication bias, these findings can still constitute ample evidence for the feasibility of rtfMRI NF in adding both healthy and clinical individuals to acquire volitionally control over the insula activity.

Successful insula regulation can be achieved with between 3 and 24 training runs. While 12 studies incorporated 3 or 4 training runs performed on a single day in healthy subjects, the remaining 13 studies (including 9 clinical studies) comprised 6 or more runs separated into 2 to 10 days (Table 2). Although the average number of training runs in clinical studies was more than in healthy subject studies (11.73 vs. 6.71 runs), clinical studies preferred to separate training runs into different single days, possibly in consideration of decreasing the training time on each day to avoid fatigue of patients on the one hand and to repeat training for a more robust and long-lasting effect at the clinical level on the other. In addition to active training runs, 13 studies included a practice/pre-training run or a transfer run without feedback (Table 2). Inclusion of a practice run can help subjects familiarize the training procedure and has been identified as a key factor in influencing training performance [95]. It has also been suggested that training success can be more reliable when a practice run is provided [36]. In the 25 qualified studies, 11 studies measured the maintenance effect in a transfer run although only two study explored maintenance effects lasting for days [74, 82] and 9 studies tested it immediately following NF training. Only 3 studies reported significant maintenance effects either in a transfer run given immediately [88, 89] or 2 days after NF training [82]. The maintenance of self-regulation ability without NF is of tremendous significance by suggesting the possibility of independent self-regulation on brain activity without continuous dependence on the MRI scanner and thus is key for a promising

Table 4. Statistics of behavioral measurement contrasts associated with NF training and brain-behavior associations.

Study	Up/Down	Behavioral measurements	EG vs. CG	Pre vs. Post	Regulate vs. Rest	Follow-up	Brain-behavior associations
Berman et al. [84]	Up	/	/	/	/	/	/
Böttinger et al. [71]	Up	CBCL/ICU/MOAS/PDS/RPQ	NS	NS	/	/	CBCL-ODD ($p = 0.038$)
Buyukturkoglu et al. [72]	Down	EDT/Disgust ratings	/	↓ ($p < 0.01$)	$p < 0.01$	EDT/Disgust ratings(ps < 0.01)[a]	/
Caria et al. [85]	Up	/	/	/	/	/	/
Caria et al. [86]	Up	Valence and arousal ratings	NS	↑ Valence ratings ($p = 0.014$)	/	/	Valence ratings ($p = 0.014$)
Emmert et al. [91]	Down	Pain stimulation ratings	/	↓ ($p < 0.01$)	NS	/	/
Frank et al. [80]	Up	Hunger ratings/TFEQ	/	NS	/	/	/
Johnston et al. [81]	Up	PANAS/POMS	/	/	/	/	/
Kadosh et al. [83]	Up/Down	/	/	/	/	/	/
Kanel et al. [88]	Up	IRI	/	/	/	/	IRI ($p = 0.051$)
Karch et al. [75]	Down	OCDS/Craving ratings	/	NS	/	/	/
Karch et al. [76]	Down	FTNR/QSU-G	/	NS	/	/	/
Karch et al. [77]	Down	BIS-11/BDI/STAXI/STAI/OCDS	STAXI ($p = 0.005$)	/	/	Abstinence rate (NS)	/
Lawrence et al. [87]	Up	Valence and arousal ratings	NS	/	NS	/	/
Linden et al. [73]	Up	PANAS/HDRS	PANAS-N ($p < 0.001$)	↓ HDRS ($p = 0.004$)	/	/	HDRS ($p = 0.033$)
Mehler et al. [74]	Up	HDRS	NS	↓(g = 1.57, 95%CI [1.04, 2.14])	-	-	/
Popovova et al. [90]	Up	Acc/RT of attention tasks	NS	↑ Alerting/ ↓ Orienting attention/ ↓ Executive control (ps < 0.05)	/	Alerting ($p = 0.01$)	RT (NS)
Rana et al. [78]	Down	VAS-C/QSU-B/CPD	/	↓ ($p < 0.05$)	/	VAS-C/QSU-B/CPD (ps < 0.05)	/
Rance et al. [93]	Up/Down	Pain stimulation ratings	/	NS	/	/	Unpleasantness ($p < 0.05$)
Ruiz et al. [70]	Up	Face emotion recognition	/	/	$p < 0.05$	/	Disgust recognition ($p = 0.018$)
Sitaram et al. [79]	Up	Valence and arousal ratings	/	-	/		/
Veit et al. [92]	Up/Down	Regulation success ratings	/	↑ ($p < 0.05$)	/	/	/
Yao et al. [82]	Up	Pain empathy ratings	$p = 0.046$	NS	/	Pain empathy ratings (NS)	Pain ($p = 0.018$)

Table 4. continued

Study	Up/Down	Behavioral measurements	EG vs. CG	Pre vs. Post	Regulate vs. Rest	Follow-up	Brain-behavior associations
Zhang et al. [89]	Up	Pain empathy ratings/ IAc/ IS/Strategy check ratings	Strategy check ratings (ps ≤ 0.035)	NS	Strategy check ratings ($p = 0.003$)	/	IAc ($p = 0.006$)
Zilverstand et al. [47]	Down	FSQ/SBQ/Anxiety ratings	Anxiety ($p < 0.05$)	Anxiety (NS)	Anxiety (NS)	FSQ/SBQ (ps < 0.001)	FSQ ($p < 0.05$)

Acc accuracy, *BDI* beck depression inventory, *BIS-11* barratt impulsiveness scale, *CBCL* child behavior checklist, *CPD* the number of cigarettes per day, *EDT* ecological disgust test, *FNTR* fagerström test for nicotine dependence, *FSQ* fear of spider questionnaire, *HDRS* 17-item hamilton rating scale for depression, *IAc* interoceptive accuracy, *ICU* inventory of callous-unemotional traits, *IRI* interpersonal reactivity index, *IS* interoceptive sensibility, *MIQ-3* movement imagery questionaire-3, *MDS-UPDRS* movement disorders society unified Parkinson's disease rating scale, *MOAS* modified overt aggression scale, *NS* not significant, *OCDS* obsessive compulsive drinking scale, *ODD* oppositional defiant disorder subscale of the CBCL, *PANAS* positive and negative affective schedule, *PDS*, pubertal development scale, *POMS* profile of mood states, *QSU-B* questionnaire of smoking urges-brief, *QSU-G* questionnaire of smoking urges, *RT* reaction time, *RPQ* reactive-proactive aggression questionnaire, *SBQ* spider belief questionnaire, *STAI* state-trait anxiety inventory, *STAXI* state-trait anger expression inventory, *TFEQ* three factor eating questionnaire, *VAS-C* visual analog scale for craving.
[a]Significant results were shown in 2 subjects.

potential in clinical translational settings. Token together, more emphasis thus should be paid on benefits of including a practice run and how to achieve more robust maintenance effect in future studies.

Similar to other rtfMRI studies, the insula was also defined structurally, functionally, or by combining both approaches. Functional localization tasks included emotional recall tasks (e.g., retrieval of autobiographical memory), passive observation of emotional/substance-related pictures, and other more specific tasks (Table 2). Although there is no evidence for the superiority of different localization approaches, a combination of structural and functional localization can take advantage of both more precise localization structurally and higher sensitivity functionally. After localization, another important step is selection of regulation strategies. In the present review, the majority of studies provided subjects with specific insula regulation strategies (15 studies), with mental imagery being the most popular strategy (12 studies). On the one hand, the advantage of providing a specific strategy is that it can provide a specific direction for subjects to work on and consequently may reduce trial and error efforts, whereas it may have disadvantages where the provided strategy is invalid or not suitable for the individual or the specific population (e.g. [96]). On the other hand, free strategies allow subjects to develop their own strategy, consequently leading to the most efficient strategy, however this approach comes at the cost of longer trial and error periods and the risk that subjects may fail to find an efficient strategy. Furthermore, a 7T fMRI study has shown that different cognitive strategies used for pain attenuation can induce different patterns of brain activity including the insula [97]. Thus, in the context of decreasing inter-subject variability induced by the use of different regulation strategies, a specific strategy, with an efficacy validated before application, may be more suitable, although it should be emphasized that currently there is no empirical evidence to confirm its superiority. Selection of regulation strategies should also take different functions of different subregions and the lateralization of the insula into consideration [98–100]. In addition, while specific strategies were used in most up-regulation studies (14 in 18 studies), free strategies were used in most down-regulation studies (7 in 10 studies), suggesting that determination of a specific regulation strategy may be more difficult for down-regulation. Regulation direction also affected the choice of whether stimuli were presented/delivered such that while stimuli were simultaneously presented during regulation/rest blocks to induce the insula activity in most down-regulation studies (9 of 10 studies), only 4 in 18 studies did this in up-regulation studies (Table 2). A variety of different types of stimuli including emotional pictures or videos, symptom-evoked pictures or painful heat stimulation were used in different studies depending on research purposes (see Table 2). It should also be noted that, for studies using the functional localization approach to define the insula (17 studies), although stimuli from the IAPS were used most frequently (10 studies), sources of stimuli were still heterogeneous. How to balance the use of validated stimulus datasets (e.g., standardized open datasets) and specific research purposes should also be considered in future studies.

In this review, the majority of the studies (21 studies) applied continuous NF, which can provide subjects the real-time NF information during the whole block and enable them to adjust their use of regulation strategies in real-time. The remaining 4 studies used intermittent feedback presented at the end of each regulation/rest block [47, 72, 78, 90], which can exclude effects of the hemodynamic response and provide individuals global information of their regulation performance [69]. This also makes intermittent feedback more suitable for MVPA-based NF aiming to modulate distributed brain patterns, including decoded NF (see [101]) and representational similarity analysis-based NF [102, 103]. Although there are no studies having explored the superiority of the two types of feedback, intermittent feedback has been found to be superior in regulating the premotor cortex and amygdala as compared to continuous feedback [104, 105]. A pilot study in 14 tinnitus patients has revealed that continuous feedback is more suitable for long-term NF training with multiple runs and intermittent feedback is more efficient for a single run NF training with respect to voluntary control over the auditory cortex [106]. However, given the limited evidence, the superiority of continuous vs. intermittent feedback should be inferred with caution and future studies are needed (cf [107, 108]).

In contrast to other factors, inclusion of a control group/condition does not affect training performance per se but is crucial to determine whether the training effect is NF-specific. In this review, half of the studies included a control group. It has been recommended that selection of a control group should be based on the specific goal of an NF training study [109]. Although it is ideal to control as many confounding effects as possible by using more control groups, it is costly and sometimes not feasible in practice. Control groups in the 13 studies used sham feedback from an unspecific or control region [74–77, 82, 87–89], no feedback [47, 73], or both of the sham and no feedback controls [85, 86, 90]. Although an entire top slice of the brain was conventionally used as the sham control region in rt-fMRI insula studies [82, 85, 86, 88, 89, 92], our recent work showed that it was not a proper control region when an interoceptive regulation strategy was used for AI up-regulation [89]. This entire top slice overlaps with the supplementary motor area which is a hub of the interoceptive network [8, 110] and thus may confound the NF training effect. This underlines the importance of proper selection of the sham control region depending on specific regulation strategies used for NF training. A control group with matched regulation strategies is a more common method that not only can minimize the number of control groups and maximize statistic power but also can simultaneously control for both placebo/unspecific effects and the use of regulation strategies (cf [109]). In addition, another way to control for confounding effects is using bidirectional regulation in a within-group design [109] which has been applied in 3 studies [83, 92, 93]. Successful bidirectional regulation together with corresponding directional behavioral/clinical changes can provide a well control for motivational and placebo effects [109].

So what behavioral and neural changes can be induced by rtfMRI NF training on insula regulation? As a prerequisite for the therapeutic potential of rtfMRI NF, behavioral/symptom-related changes associated with training success have been measured in 22 among the 25 qualified studies. However, significant behavioral/symptom-related changes were only found in 13 of them, including ratings to emotional stimuli, painful stimulation, or perceived regulation success in healthy subjects [82, 86, 89–92] and improvement in symptom-related indices in psychiatric disorders including spider phobia [47], schizophrenia [70], OCD [72], MDD [73, 74], and addictions [77, 78]. Importantly, behavioral changes were also found to be correlated with NF-induced changes in insula activity in 9 studies involving both healthy [82, 86, 88, 89, 93] and clinical populations [47, 70, 72, 73]. Significant brain-behavior correlations can provide further evidence that behavioral/symptom-related changes are specific to NF training. There is also evidence for a sustained decrease in symptom severity in patients with OCD [72], smoking addiction [78] and spider phobia [47] varying from 1 day to 6 months after NF training in follow-up measurements (Table 4). However, in contrast to the majority of studies (21 studies) showing training success of insula regulation, there are no comparable studies demonstrating parallel behavioral/symptom-related changes (13 studies). These findings on the one hand verify the therapeutic potential of rtfMRI NF training but on the other hand highlight the need to optimize NF training protocol for more robust behavioral/symptom-related changes.

In addition to changes at the behavioral level, 10 studies have also examined neural changes indexed by functional connectivity and all of them revealed increased functional connectivity of the AI, mainly with the medial and dorsal lateral prefrontal regions and the cingulate cortex within the regulatory control network. Acquisition of voluntary control over brain activity by NF training is particularly involved in the regulation learning process and consequently the underlying regulatory and learning networks [111]. Similar increased functional connectivity with these networks has also been found in previous rtfMRI studies targeting other regions [46, 112, 113]. These findings suggest that successful regulation may share a similar neural modulation mechanism underpinned by functional coupling between different target regions and similar regulation and learning networks. In contrast to the more convergent findings on increased functional connectivity during NF training, preliminary findings in 2 studies on rsFC changes induced by NF training are divergent [75, 82]. Changes of rsFC induced by NF training have also been found in previous rtfMRI studies targeting other regions either in healthy [114] or clinical populations [46, 61, 115, 116], indicating possibilities that NF training can also alter intrinsic organization of brain networks.

There are some limitations in the present study. First, characteristics such as feedback types, training protocols, and definition of training success in different studies were highly heterogeneous, which did not allow a fully quantitative meta-analysis and therefore mainly a qualitative review was conducted. Although we conducted an exploratory meta-analysis and showed a medium effect size of NF training, any inferences related to this finding should be made with caution given the small sample size of qualified studies (11 studies). Second, given the nature of rtfMRI studies, training efficacy is mainly determined by estimating activation changes in a pre-defined insula region and therefore coordinate-based meta-analyses employing the activation likelihood estimation approach requiring whole-brain results are also not appropriate for the scope of the present study. Third, the potential of publication bias did not allow statistical inferences with respect to determining the most efficient training characteristics. Similar to publication bias in other fields [117, 118], most of available rtfMRI insula publications were based on positive results. Indeed our exploratory analysis using the Egger's test showed a significant publication bias, which can not be excluded and may also further inflate the effect size of our exploratory meta-analysis [65, 119]. To mitigate publication bias we additionally conducted a search for registered reports [65, 120, 121], but found no registered report that targeted the insula for rtfMRI NF training. Hence, the ratio of training success can still be an inflated indicator of training efficacy and comparisons between specific characteristics that may affect training success are therefore of limited information (cf [36]). This further did not allow us to draw specific conclusions on how to optimize selection of characteristics and principles of NF protocol design.

In conclusion, the present review provides a comprehensive overview of progress in the field of insula regulation based on rtfMRI NF training based on 25 qualified studies. Results showed that rtfMRI NF is an effective approach to assist individuals in learning voluntary regulation of insula activity in both healthy and clinical populations, particularly given the evidence of the maintenance effect of self-regulation ability observed in transfer runs without NF. Successful insula regulation can induce corresponding changes not only in behavioral/symptom-related indices that are closely associated with insula function but also in neural responses such as functional connectivity. Together with the sustained symptom severity improvement as revealed by follow-up measurements, these findings suggest a promising clinical application potential of rtfMRI NF in normalizing alterations in psychiatric disorders characterized by insula dysfunction. Of note, there are fewer studies showing parallel behavioral/

symptom-related changes compared with studies showing training success of insula regulation, possibly due to high heterogeneity of characteristics used across studies and indicating a need for optimizing the NF training protocol enabling more robust training effects particularly in clinical populations. Those may be achieved via developing novel regulation strategies that are more suitable for patients, determining the optimal setup of training runs separated into different days, or optimizing individualized localization of target subregions associated with clinical symptoms. Although design of training protocols such as whether a transfer run and stimuli are used should be based on specific research purposes, principles for inclusion of a well-designed control group/condition, statistical analyses and reporting results following standardized criteria and a priori determination of sample and effect sizes as well as pre-registration of studies are highly recommended (see also [63, 69, 120–122]). While preregistration studies and particularly comprehensive study preregistrations entail a complete analysis plan and document any deviations between the preregistration and the final results and registered reports are peer-reviewed based on a comprehensive preregistration protocol as required by specific journals. They therefore allow to increase the transparency, credibility, and reproducibility of studies [65, 121, 123, 124]. However, comprehensive study preregistrations and registered reports are still rare in the rtfMRI NF field (e.g., [125, 126]). Taken together, we believe our review will inspire and inform both fundamental research and therapeutic translation of rtfMRI NF training as an intervention in mental disorders particularly those with insula dysfunction.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

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