Volitional Control of Anterior Insula Activity Modulates the Response to Aversive Stimuli. A Real-Time Functional Magnetic Resonance Imaging Study

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Background: A promising new approach to cognitive neuroscience based on real-time functional magnetic resonance imaging (rtfMRI) demonstrated that the learned regulation of the neurophysiological activity in circumscribed brain regions can be used as an independent variable to observe its effects on behavior. Here, for the first time, we investigated the modulatory effect of learned regulation of blood oxygenation level-dependent (BOLD) response in the left anterior insula on the perception of visual emotional stimuli.

Methods: Three groups of participants ($n = 27$) were tested: two underwent four rtfMRI training sessions receiving either specific ($n = 9$) or unspecific feedback ($n = 9$) of the insula’s BOLD response, respectively, and one group used emotional imagery alone ($n = 9$) without rtfMRI feedback. During training, all groups were required to assess aversive and neutral pictures.

Results: Participants able to significantly increase BOLD signal in the target region rated the aversive pictures more negatively. We measured a significant correlation between enhanced left anterior insula activity and increased negative valence ratings of the aversive stimuli. Control groups performing either rtfMRI training with unspecific feedback or an emotional imagery training alone were not able to significantly enhance activity in the left anterior insula and did not show changes in subjective emotional responses.

Conclusions: This study corroborates traditional neuroimaging studies demonstrating a critical role of the anterior insula in the explicit appraisal of emotional stimuli and indicates the adopted approach as a potential tool for clinical applications in emotional disorders.

Key Words: Aversive stimuli, insula, real-time fMRI, self-regulation

Traditionally, studies in affective neuroscience investigate neural processes underlying emotions by correlating brain activity with the presentation of emotion-inducing stimuli or when participants imagined or recalled emotionally relevant scenarios. The emotional stimulus is manipulated as the independent variable and the neural response recorded as the dependent variable. This approach has generated a large amount of data showing specific relationships between brain activity and emotional behavior (1–6). Recently, a promising noninvasive technique, real-time functional magnetic resonance imaging (rtfMRI) inspired a different approach to cognitive neuroscience and demonstrated that learned control of the local brain activity could be used as an independent variable to observe its effects on behavior, which then functions as the dependent variable (7,8). By using rtfMRI, human participants can be trained to regulate their brain activity in circumscribed regions in the presence of contingent feedback of blood oxygenation level-dependent (BOLD) response (9–12). Recent data indicate that learned modulation of neural activity leads to changes in cognitive and motor performance, pain perception, and language processing (13–16). These findings indicate that rtfMRI could complement traditional neuroimaging techniques by providing more causal insights into the functional role of circumscribed brain regions in behavior through direct manipulation of the brain system responsible for an emotional response. So far, very few studies reported an association between enhanced activity in localized brain regions and changes in emotional behavior (16,17). Moreover, our recent findings on self-regulation of BOLD activity in the anterior insula (18) prompted the question whether its learned control induces changes in the response to emotional stimuli.

Several studies have gathered evidence for the involvement of the anterior insula in emotional processing (2,19–28). Wager et al. (24) observed predominant left insula activity during tasks associated with negative or withdrawal-related emotions. Increased activity in the left insula was also associated with reported negative valence of emotional pictures (29,30).

We investigated the modulatory effect of BOLD response in the left anterior insula on the perception of visual emotional stimuli. In particular, we hypothesized enhanced subjective responses to aversive pictures associated with the learned increase of insula activity through rtfMRI training. Three groups of participants were tested: two underwent four rtfMRI training sessions receiving either specific (EX group) or unspecific feedback (SH group) of the insula’s BOLD response, respectively, and one group used emotional imagery alone (MI group) without rtfMRI feedback. During training, all groups were required to assess aversive and neutral pictures.

Establishing a relationship between the modulation of neural activity in anterior insula and a specific emotional behavior would not only complement the traditional neuroimaging approach but may also encourage a neurobehavioral treatment of emotional disorders.
Figure 1. Experimental design. Sessions consisted of five regulation blocks (30 sec) alternating with six baseline blocks (30 sec) both followed by an International Affective Picture System (IAPS) picture presentation block (9 sec) and a rating block (12 sec). During rating blocks, participants were shown the Self-Assessment Manikin (SAM), which allows them to evaluate emotional valence and arousal. Both valence and arousal dimensions vary along a 9-point scale. Selection of the subjective rating was performed by positioning a red outline on the chosen number on each of the two scales, presented in close succession. Subjects were provided with two buttons allowing movements of the cursor in the left and right direction. IAPS, International Affective Picture System.

Methods and Materials

Experimental Procedure

Experimental Group. The experimental protocol consisted of four functional magnetic resonance imaging (fMRI) (Supplement 1) sessions (S1–S4) performed on 1 day. Sessions consisted of five regulation blocks alternating with six baseline blocks both followed by a picture presentation block and a rating block (Figure 1). During the regulation block (30 sec), which was indicated by a red background, participants were asked to increase insula activity, while during baseline (30 sec), indicated by a blue background, they had to return the activity to the baseline level.

Subjects were guided to modulate the BOLD response in the target region of interest (ROI) (Supplement 1) by a graphical thermometer displaying changes of BOLD activity with increasing or decreasing numbers of bars (Figure 1). The number of available bars was limited. Bars above the baseline level of activation were colored in red, while those below the baseline level were colored in blue. Thermometer bars were updated every 1.5 sec when a new BOLD signal from the ROIs was available (18).

Participants were informed that the colored feedback bar reflects their ongoing “brain activity” and that they should try to increase the vertical length of the red bar as much as they could during the regulation blocks. They were told that participants could use emotional imagery to drive the feedback bar but that people vary in the strategies they use: “you are free to try any other strategy to move the feedback bar except movements, tension, and facial expression changes.” After both regulation and baseline blocks, one emotionally negative or neutral picture from the International Affective Picture System (IAPS) (31–33) was presented for 9 sec and rated using a button-based control device inside the magnetic resonance imaging scanner (Figure 1). Pictures were evaluated in terms of subjective emotional valence and arousal using the Self-Assessment Manikin (SAM) (34). The Self-Assessment Manikin is a nonverbal pictorial assessment for measuring pleasure, aversion, and arousal associated with a person’s affective reaction. Valence and arousal dimensions vary along a 9-points scale (valence: from 1 = extremely negative to 9 = extremely positive; arousal: from 1 = calm to 9 = exciting). Before the experiment, participants werebriefed about the experimental tasks and SAM ratings and were trained to rate the pictures. Subjects were presented with the two SAM valence (6 sec) and arousal (6 sec) scales in close succession. The final selection of each subjective rating was performed by positioning a red outline on the chosen level on the scale. Participants were provided with two buttons allowing movements of the cursor in the left and right directions.

The pictures presented to the participants consisted of 20 aversive and 20 neutral pictures from IAPS (Supplement 1). Picture selection was based on normative ratings (31); mean values of aversive pictures were 3.26 ± 0.78 SD and 4.93 ± 0.47 SD for valence and arousal, respectively. Moderately aversive/threat-related pictures were chosen to avoid ceiling effects and allow differential ratings. Mean values of neutral pictures were 4.84 ± 0.32 SD and 2.33 ± 0.40 SD for valence and arousal, respectively.

Pictures were pseudorandomized such that no significant difference in valence and arousal ratings was present between pictures after regulation and baseline blocks and between sessions. Additionally, presentation of the pictures was randomized across subjects. Each session lasted about 9 minutes.

Control Groups. The SH group performed identical training and received the same instructions. Participants received sham feedback comparable in terms of signal magnitude and variability but not contingent on BOLD signal in the target ROI. Instead, the feedback provided information about the average activity in a large brain area not encompassing the left and right insula.

The MI group was trained to assess the effects of repetitive use of emotional imagery. They were instructed to recall memories and imagery of personally relevant affective episodes during regulation blocks but no feedback about BOLD was given. The MI group was presented with the thermometer frame without rtfMRI information (no bars were shown). Apart from the missing movement of the feedback bar, conditions were identical in all three groups. Similar to the EX group, both SH and MI groups were presented with IAPS pictures following imagery blocks (30 sec) and performed SAM ratings.

Data Analysis

fMRI. Offline ROI and whole-brain analyses were performed using MarsBar toolbox (http://marsbar.sourceforge.net) and SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom), respectively. Functional echo planar imaging volumes were realigned, normalized into Montreal Neurological Institute (MNI) space, smoothed spatially (9-mm full-width half-maximum Gaussian kernel) and temporally (cutoff period 256 sec). Hemodynamic response amplitudes were estimated using standard regressors, constructed by convolving a boxcar function representing the blocks duration with a canonical hemodynamic response function using standard SPM2 parameters. Motion parameters were also included into the general linear model as covariates to account for variance caused by head motion. As a first-level analysis, contrast images for regulation and baseline were created session by session for each subject. These images were then entered into a second-level (random effects) analysis.
The resulting statistical parametrics were thresholded at \( p < .001 \), corrected at cluster level with extent threshold of \( k = 10 \) voxels; brain regions were labeled anatomically according to Tzourio-Mazoyer et al. (35).

The averaged percentage signal change in the targeted ROI (left insula) and its homologous in the opposite hemisphere (right insula) during regulation with respect to baseline was calculated over sessions for both experimental and control groups. The influence of contingent rtfMRI feedback on learning to regulate activity in left anterior insula was compared among the groups by a repeated measures \( 3 \times 4 \) analysis of variance (ANOVA) with group (EX, SH, MI) as between factor and session (S1 to S4) as within factor. Paired-samples \( t \) tests were used as post hoc tests to compare the first and the last session in each group. Additionally, a linear regression of the averaged percentage BOLD signal change over sessions was used to test for session by session increase as an index of learning. Paired \( t \) tests and linear regression were also performed on the averaged percentage signal change of the right insula to examine bilateral insula activation, which often has been reported in traditional neuroimaging studies (23,24,29,30).

**Subjective Responses and Correlation with fMRI Data.** The difference in ratings of the emotional visual stimuli presented after regulation with respect to baseline were calculated individually for valence and arousal of aversive and neutral stimuli; these differences served as dependent variables and were assessed across sessions and groups. To this aim, separate \( 3 \times 4 \) repeated measures ANOVAs with group (EX, SH, MI) as between factor and session (S1 to S4) as within factor, respectively, were performed. Subsequently, separate paired-samples \( t \) tests were carried out as post hoc analyses to compare the dependent variables in the first and last sessions for each group.

Finally, Pearson bivariate correlation was performed to verify the association between the behavioral ratings and the averaged percentage signal change in the targeted ROI. Differences of percent BOLD signal between the regulation and baseline conditions and of the subjective ratings of the emotional pictures between the baseline and regulation conditions were considered over sessions. Statistical analysis of the percentage signal change and behavioral data analysis were accomplished using the statistical package SPSS 17.0 (SPSS, Inc., Chicago, Illinois).

**Results**

**ROI Analysis**

The averaged percentage signal change in the left anterior insula measured during each session in EX and the two control groups is reported in Figure 2. A significant group \( \times \) session interaction effect, \( F(2,22) = 11.07, p = .001 \), emerged from the ANOVA on the percent BOLD signal change in the target ROI. Neither group nor session significant main effects were found. Paired-samples \( t \) tests highlighted a significant increase from S1 to S4 \((t = 3.22, \text{df} = 8, p = .012)\) in the EX group, no significant differences between sessions in the SH group \((t = 1.89, \text{df} = 8, ns)\), and a significant decrease in the MI group \((t = 2.62, \text{df} = 8, p = .034)\).

Additionally, linear regression showed a progressive enhanced activity in the target area across training sessions in the EX group, indicating a learning effect \((y = .28x - .29, t = 2.61, p = .014)\). The SH group did not show a similar learning pattern \((y = -.19x + .62, t = -1.32, ns)\), whereas the MI group showed a significant decreasing activation over sessions in the target ROI \((y = -.20x + .77, t = -3.40, p = .002)\). Analysis of variance of

![Figure 2. Brain activity in the left and right anterior insula in the experimental and control groups during real-time functional magnetic resonance imaging training. Percent signal change was calculated by computing the difference of the percent BOLD signal during regulation and baseline for each participant and then averaging across all the participants. Increased percent BOLD in the target area over sessions is observed in the experimental group only. The two control groups trained with sham feedback and using mental imagery alone were not successful in learning to regulate insula activity. No percent BOLD increase was observed in the right insula in any group. *Significant changes \((p < .05)\) in session 4 with respect to session 1. Bars represent group mean and standard error of the mean. BOLD, blood oxygenation level-dependent; EX, group receiving specific feedback; L, left; MI, group using emotional imagery alone without feedback; R, right; S1, session 1; S2, session 2; S3, session 3; S4, session 4; SH, group receiving unspecific feedback.](www.sobp.org/journal)

the right anterior insula (Figure 2) showed significant group \([F(2,22) = 15.88, p < .001]\) and session \([F(2,22) = 12.17, p = .002]\) main effects and group \( \times \) session interaction effect \([F(2,22) = 9.32, p = .001]\). Paired-samples \( t \) tests between groups within first and last session revealed that whereas during S1 no differences were observed, during S4 right insula BOLD signal change in the EX group was higher than in the SH \((t = 4.01, \text{df} = 16, p = .001)\) and the MI \((t = 5.11, \text{df} = 16, p < .001)\) groups, which did not differ from each other.

Additionally, paired-samples \( t \) tests within each group showed no significant difference in the right anterior insula between S1 and S4 for the EX group, whereas both control groups showed a significant decrease \((\text{SH: } t = 2.77, \text{df} = 8, p = .040; \text{MI: } t = 3.19, \text{df} = 8, p = .015)\). A linear regression resulted in a no significant effect in both EX \((t = .97, p = .339)\) and SH \((t = -1.95, p = .064)\) groups, while in the MI group, similarly as for the left insula, a significant decrease over sessions was observed \((t = -3.17, p = .003)\).

**Whole-Brain Analysis**

Whole-brain random effect analysis confirmed the results of the ROI analysis (Figure 3): training resulted in a significantly increasing activation cluster in the targeted left anterior insula over sessions \((\text{MNI: } = -43, 16, 0; \text{S1 and S2: no activation observed, } p < .001; \text{S3: } t = 5.52, p < .001; \text{S4: } t = 7.43, p < .001)\); additional activations throughout the training were observed in the right insula \((\text{MNI: } = 43, 13, 0; t = 8.99, p < .001)\), the cingulate cortex \((\text{MNI: } = 0, -13, 20; t = 7.45; \text{MNI: } = 7, 26, 30; t = 7.25, p < .001)\), and the left dorsolateral prefrontal cortex \((\text{MNI: } = -33, 20,\)
10; t = 7.50, p < .001) during S1; the left middle frontal gyrus (MNI = −26, 40, 20; t = 7.45, p < .001) and the right insula (MNI = −26, 40, 20; t = 7.45, p < .001) during S2; the right insula (MNI = 43, 20, −5; t = 7.00, p < .001) during S3; and the left superior temporal gyrus (MNI = −63, −40, 20; t = 7.58, p < .001) and the right insula (MNI = 46, 13, −5; t = 8.13, p < .001) during S4. Separate ROI analysis of the additional active areas showed no significant training effect (Supplement 1).

Behavioral Data

Absolute mean ratings for all groups are reported in Figure 4. To assess changes over sessions of the emotional stimuli appraisal after regulation relative to baseline blocks, the average difference of the picture ratings (valence and arousal) between these two conditions was calculated separately for all groups. The ANOVAs revealed a significant group × session interaction effect, F(2,78) = 6.13, p = .004, for the differences in valence ratings of aversive pictures; neither group nor session significant main effects were found. Moreover, no main or interaction effects emerged for the valence of the neutral pictures; neither group nor session significant main effects were found. Moreover, no main or interaction effects emerged for the valence of the neutral pictures and for the arousal of both aversive and neutral pictures. Paired-samples t test (two-tailed) highlighted a significant effect between S4 and S1 of the differences in valence ratings of aversive pictures (t = 2.75, p = .014) in the EX group exclusively, that is aversive stimuli were rated more negatively after regulation with respect to baseline in the last session in this group (Figure 5).

Brain-Behavior Association

Pursuing the relationship between brain activity and rtfMRI training associated modulation of emotional assessment and driven by the observed behavioral results, we performed a correlation analysis between the averaged percent BOLD changes in the target ROI and the differences in valence ratings. The observed significant correlation (Pearson r = .407; df = 36; p = .014 two-tailed) indicates that increased activity in the left anterior insula is associated with decreasing valence ratings—more negative—of aversive pictures (Figure 6).

Discussion

The present study demonstrates that learned control of BOLD signal in the left anterior insula influences the behavioral response to emotional stimuli. Participants in the EX group, who learned to significantly increase BOLD signal in the target region, rated aversive pictures more negatively after regulation. The larger the positive difference in the BOLD activation in the anterior insula between regulation and baseline conditions, the higher is the level of perceived negative emotion of the aversive stimuli. Conversely, the smaller or more negative this difference of the BOLD, the lower is the level of perceived negative emotion of the aversive stimuli. The SH and MI control groups, unable to successfully achieve control of the target brain region over time, showed no significant changes in the evaluation of the emotional stimuli.

A reduction of BOLD response in left anterior insula over time was observed in both control groups, though a significant effect was observed in the MI group only. This effect may be due to habituation after repeated recall of emotional memories (36). Costa et al. (37) observed BOLD decrease in mesolimbic reward structures, including the amygdala, which has projection to and from insula (38,39) during unpleasant imagery and interpreted it as inhibition of appetitive circuitry. Moreover, previous studies reported a reduced BOLD response in the targeted ROI when sham or unspecific rtfMRI feedback was provided (14).

Results from the control groups indicate, first, that learned self-regulation of the BOLD signal in the target region does not result from general arousal and/or global brain activation. Second, an unspecific feedback or mental imagery performed in the absence of contingent feedback is not adequate for learning to modulate the insula activity. As previously indicated (18), a combination of cognitive strategies (imagery) and real-time fMRI information drives participants to acquire successful control in a few training sessions. Whether the combination of emotional imagery and contingent feedback are sufficient to achieve voluntary control cannot be decided on the basis of these results. Nevertheless, time-contingent feedback of the physiological response (BOLD) constitutes a necessary ingredient of brain self-regulation.

In the postexperimental interview, most of the participants reported to have achieved BOLD signal control in the target ROI by using mental strategies focused on recollection and re-experience of salient emotional life episodes. This is in line with the literature showing the anterior portion of the insula to be active during emotional recall and self-generated emotions and suggesting its preferential role in the evaluative, experiential, or expressive aspects of internally generated emotional and visceral responses (2,3,24,40–42).

Training to volitionally regulate the insula leads to a decrease of the number of active clusters and to more focused brain activations. This result may represent a further indication of learning. The network involved during rtfMRI training included the dorsolateral prefrontal cortex, presumably responsible for retrieval of emotional memories (43); the cingulate cortex, implicated in emotion processing (2); the right insula as a site for

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Figure 3. Random effects analysis on the experimental group confirmed an increased blood oxygenation level-dependent magnitude in the left anterior insular cortex over time. A significant increased activation (p < .001 corrected at cluster level with extent threshold of k = 10 voxels) was observed during the third (t = 5.52) and the fourth (t = 7.43) sessions in the target area, Montreal Neurological Institute = −43, 16, 0. Activation maps are projected on a single-subject T1 template at the coordinate z = 0. S1, session 1; S2, session 2; S3, session 3; S4, session 4.
the meta-representation of interoceptive states (44,45); the left inferior frontal gyrus; and the left superior temporal gyrus for language-related recall of emotional episodes (46). No significant increase over sessions was observed in these additional brain areas.

**Self-Regulation of Localized Brain Activity and Functional Specificity**

This study reinforces the rtfMRI-based approach as a useful tool to investigate brain-function relationships. Self-regulation of the anterior insula activity was associated with changes in subjective ratings of valence, but not of arousal, of emotional stimuli. Participants perceived the aversive pictures more negatively over sessions, meaning that their sensitivity increased with learned regulation. No changes in the perceived intensity of the emotional pictures were observed over sessions, as indicated by stable arousal ratings. Though, the arousal might have been masked by an attenuation effect due to the long presentation of emotional pictures (9 sec) or to continuous emotional and cognitive effort for achieving successful regulation.

In line with previous literature (29,47,48), our results indicate that different aspects of the emotional response might be mediated by different brain circuits. Emotional affect has been conceptualized along two main dimensions: valence, describing the extent of positive/pleasant/appetitive versus negative/aversive/defensive, and arousal, which describes the intensity of activation (5,6,32,33). Neuroimaging studies (5,6,29,47) suggested a dissociation of the brain mechanisms underlying valence and arousal of emotional stimuli. However, whereas for processing...
arousal of the emotional stimuli the amygdala seems to play a preferential role, for valence dimension, several regions including bilateral insula and mediofrontal and orbitofrontal cortex have been indicated (5, 6, 34, 47, 48).

Anders et al. (29) observed that verbal reports of negative emotional valence varied with left insular activity, whereas peripheral physiologic and verbal responses, along with the arousal dimension, varied with thalamic and frontomedial activity. Moreover, Viitikainen et al. (30) showed that BOLD signal in the bilateral insula correlated positively with valence ratings of unpleasant IAPS pictures and negatively with valence ratings of pleasant pictures. On the contrary, a mutual interaction between valence and arousal has been observed. Some studies reported greater negative ratings correlating with increased arousal within structures such as the amygdala, nucleus accumbens, and fusiform and other extrastriate visual sensory areas (5, 6, 48).

In our study, no indications about changes of the intensity dimension of emotional state of the participants, either aroused or calm, could be directly observed, as no peripheral physiological signals were measured. Future rtfMRI studies on emotional processing might clarify this point by including direct measurements of the arousal state.

Interestingly, false feedback of increased heart rate—associated with changes in neural activity in the right anterior insula, bilateral mid-insula, and amygdala—has been shown to result in increases in emotional intensity ratings of neutral faces (49). However, heart rate feedback, even when false, is expected to affect emotional appraisal because of its strong sensory awareness component, while fMRI feedback acts in a more indirect and covert fashion, as subjects are not aware of brain metabolic responses. In our study, right insula activity was measured throughout the rtfMRI training but no differences in the arousal dimension were observed.

Among the multitude of findings of insula involvement from the fMRI literature in emotion, empathy, and interoceptive awareness, the issue of laterality is still controversial. Craig (50) postulates a bias for the right anterior insula in negative affect and for the left insula in positive affect. In contrast, Wager et al. (24) observed predominant left insula activity associated with withdrawal and negative emotion-related behavior. In our study, participants generated both positive and negative memories during the training, making it difficult to group them post hoc according to the valence of the imagined emotional experiences. A study disambiguating the effect of specific emotional strategies, as previously suggested (41, 51), might yield insight into a possible differentiation between representations of positive and negative emotion-related bodily states in the right and left insula.

Overall, our results confirm the prominent role of the anterior insula in emotional processing, specifically in the explicit appraisal of emotional and body-visceral stimuli (44, 52). Previous studies demonstrated the involvement of anterior insula, along with the anterior cingulate cortex and ventral medial prefrontal cortex, in the secondary processing of emotional experience through the integration of interoceptive signals with the external context (41, 52, 53). On the other hand, a circuit encompassing the amygdala and the ventral striatum was implicated in primary processing of withdrawal and approach behavior (54). The anterior insula forms an explicitly accessible functional representation of interoceptive bodily states and generates regulatory signals necessary to maintain bodily homeostasis (1, 25, 44, 45, 51). It was also postulated that anterior insula activity represents a limbic substrate for the subjective awareness of emotional states (55).

This hypothesis is supported by studies observing increased insula activity to both unpleasant and pleasant feelings evoked by emotional stimuli (44, 52). Here, the effect of the enhanced left insula activity on appraisal of negative emotional stimuli has been confirmed, though, as positive stimuli were not presented, specificity of this association has to be tested.

Clinical Perspectives

The rtfMRI-based approach might be relevant for clinical applications, as already indicated by deCharms et al. (14). Specifically, our study indicates a potential application of the self-regulation of insula activity for treatment of emotional disorders in light of the insula’s role in fear conditioning both in healthy subjects and patients (56–58). Critchley et al. (56) reported a modulation of the insula activity by conscious awareness of paired conditioned stimuli during fear conditioning.

The insula seems to be crucial in anticipatory anxiety induced by exposure to aversive stimuli (20, 59). A recent meta-analysis of neuroimaging studies suggested a common exaggerated engagement of fear circuitry, including amygdala and insula hyperactivity, in anxiety disorders (60). Studies on anxiety-prone subjects reported increased amygdala and insula activation during both anticipation and observation of aversive pictures (61, 62). It has been hypothesized that insula hyperactivity might be a common feature in persons with elevated trait anxiety and therefore might represent a marker for anxiety proneness (63). Finally, the anterior insula’s hypoactivity has been reported to be associated with lack of aversive anticipatory arousal in psychopathy (57, 58), whereas its hyperactivity was observed in social phobia (57). Together, these findings indicate the insula as a candidate region to develop rtfMRI-based treatment for patients suffering from emotional disorders.


