Real-time fMRI neurofeedback and self-regulation of negative emotional affectivity

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Abstract

Research showed that negative emotions not only lead to psychological problems and mental disorders such as anxiety and depression, but they can also cause impairment of physical health including tobacco dependence, coronary heart disease and cancer. Real-time functional magnetic resonance imaging (rtfMRI) neurofeedback is a new technique that involves training patients to control the activation in specific brain regions. The method involves individualizing the brain area where the activity needs to be regulated and providing the participant with a real-time feedback about the activation. rtfMRI neurofeedback has been used to train subjects to regulate brain regions involved in negative affectivity. The most important brain regions involved in emotional regulation are the amygdala, the anterior cingulate cortex (ACC), and the insula. The paper describes current discoveries in which participants learned to regulate these brain areas giving satisfactory evidence for emotional regulation with rtfMRI, and proposes new challenges for future research.

Introduction

Negative affectivity is not always easy to define. Psychologists generally describe negative emotions as unpleasant feelings, which are evoked in people to express a negative affect towards an event or person (Watson & Clark, 1984). In this review, we refer to this definition. Negative emotions include feelings such as fear, anger, anxiety, hostility, hopelessness, and depression. Depression is a negative emotion which is associated with low arousal. It generally entails lack of interest in activities, depressed mood, fatigue, and in its extreme cases suicidal thoughts (American Psychiatric Association, 2013). Depression is closely related to the feeling of anxiety. In fact, scientists have found that depressed patients often report feelings of anxiety (Nitschke, Heller, Imig, McDonald, & Miller, 2001). Symptoms such as fatigue are often included also in the definition of anxiety (American Psychiatric Association, 2013). However, anxiety is associated with positive arousal and additional symptoms such as irritability, sleep disturbance, and difficulty in thinking or concentrating. Hostility is related to anger and is

exhibited by patients with negative attitudes about others (Eckhardt, Norlander, & Deffenbacher, 2004). The causes leading to the development of negative emotions are multiple. Some studies have found empirical evidence for genetic causes (Todd et al., 2013), yet others have shown that the environment, and variables such as low social economic status, are also likely to be the origin of negative affectivity (Gallo & Matthews, 2003). Another study investigated the effects of acute laboratory stressors, such as speech or handgrip, on emotional states and cardiovascular responses (Feldman et al., 1999). Subjects reacted to stressors with both increased negative emotion and increased cardiovascular response.

Negative emotions cause the production of stress hormones such as cortisol and adrenaline. While they have little or no effect in the short term, a great deal of evidence suggests that enduring negative emotional states may impair both physical and psychological health (Lyubomirsky, Tucker, Caldwell, & Berg, 1999). Research on young adolescents investigated the health outcomes of girls with conduct disorder, depression, and anxiety (Bardone et al., 1998). The study demonstrated that depression predicts adult tobacco dependence and medical problems, and anxiety predicts medical problems as adults. Growing evidence supports the hypothesis that bad feelings, and especially hostility and anxiety, influence the development of specific diseases such as coronary heart disease and cancer (Kubzansky & Kawachi, 2000; Makarenko, 1988). These diseases are one of the leading causes of death in industrialized western societies, suggesting that finding treatments for improving negative emotional states is of primary importance.

Traditional psychiatric therapies for emotion regulation such as Cognitive Behavioral Therapy (CBT) have been widely used in the past to regulate emotions. Fresco, Mennin, Heimberg, & Ritter (2013) developed Emotion Regulation Therapy (ERT) in which they integrate CBT, emotion-focused interventions, and mindfulness. Their therapy was demonstrated to be particularly efficient in regulating emotions and more specifically to treat patients with Generalized Anxiety Disorder. Despite their success, these and other therapies for emotion regulation have focused on symptomatic rather than neurophysiological criteria.

To investigate neurophysiological criteria, Real-time functional magnetic imaging (rtfMRI) neurofeedback was introduced. One of the main purposes of this technique is to train subjects to up or down regulate the activity of a specific region-of-interest (ROI) in the brain by observing real-time feedback (Sulzer et al., 2013). fMRI shows the blood oxygenation level dependent (BOLD) signals in the brain. During specific tasks, active brain regions consume more oxygen allowing fMRI to localize the neural activity (Arthurs & Boniface, 2002). For this reason, neurofeedback can establish causal links between brain activation and behaviour.

Furthermore, the possibility to regulate different regions in the whole brain suggests a great number of applications, for example the regulation of brain areas involved in emotional regulation.

Therefore, the purpose of this paper is to provide a review on the current progress of the use of neurofeedback for self-regulation of emotional states. The paper begins with a general overview on the functionality and study design of rtfMRI neurofeedback. Following this, brain regions which are relevant for the study of emotions are described. Finally, the paper reviews the research and discoveries about the link between neurofeedback and affective sates regulation.

Real-time fMRI neurofeedback

The principle of neurofeedback can be applied to a wide range of technologies. Techniques such as electroencephalogram (EEG) provides scientists with a non-invasive method to measure the level of activity in the brain. EEG offers a very high temporal resolution but a relatively low spatial resolution (Pascual-Marqui, Michel, & Lehmann, 1994). In contrast, fMRI has a finer spatial resolution and the capability to cover the whole brain, and it thus permits researchers to obtain more detailed information about the association between the brain and its functionalities (Debener, Ullsperger, Siegel, & Engel, 2006). fMRI has the possibility to be used as a brain-computer interface (Sorger, Reithler, Dahmen, & Goebel, 2012) and in real-time neurofeedback implementations. rtfMRI neurofeedback has a broad spectrum of applications due to its ability to teach people to control functioning brain areas. In order to reach this objective, Sulzer et al. (2013) described an experimental framework, used in neurofeedback studies, which consist of few major steps (Figure 1). Firstly, the region of the brain that needs to be trained must be initially localized. Participants are thus asked to perform tasks that would activate the ROI in the brain while lying inside an fMRI scanner. Since these brain areas are similar, but not identical between individuals, researchers usually individuate and record the specific brain regions activated for each participant. The second step involves presenting the activity in the ROI to the subject in real-time, who is instructed to up-regulate, or down-regulate, the activation in the target region. The feedback is usually presented through a screen as a thermometer display. Other researchers utilized other methods for providing feedback to participants such as visual reality (Christopher deCharms et al., 2005; Goebel, Sorger, Kaiser, Birbaumer, & Weiskopf, 2004). The time required from individuals to learn the tasks varied between the studies. However, some research has demonstrated that one single day training with rtfMRI feedback is enough to achieve learning (Christopher deCharms et al.,

2005; Weiskopf et al., 2004). The third and final step begins once the participants achieve enough control on the activation. In this last phase, subjects are tested in different settings without the feedback to understand whether they are able to maintain the new ability outside from the scanner.

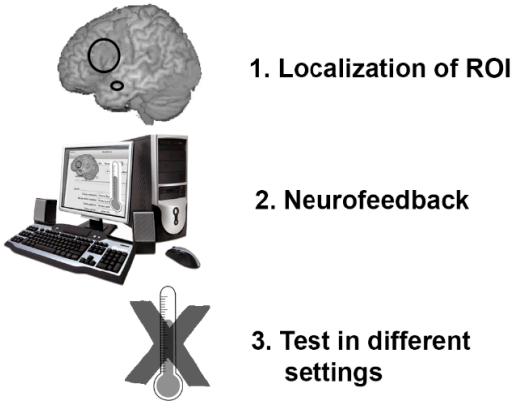

Figure 1. The three steps in rtfMRI research: 1. the brain area that needs to be trained is localized. 2. a feedback showing the activity of the brain region localized in step 1 is presented to the subject who is asked to regulate it. 3. the feedback is removed and the maintenance of the new ability is verified in different settings.

No potential risks for fMRI-use have been found in 20 years of application. Studies also regard MRI and fMRI as risk-free methods (Bourland, Nyenhuis, & Schaefer, 1999; Schenck, 2000). However, it is important to realise that for some participants, fMRI is not possible. For example, subjects with metal implants are not allowed to enter a MRI scanner because the strong magnetic field could interfere with the metal implants causing substantial image artefacts, including signal loss and geometric distortion (Hargreaves et al., 2011).

Emotions in the brain

The previous section described the steps that researchers usually take while implementing rtfMRI neurofeedback studies. In order for a researcher to use this technology to regulate negative affectivity, ROIs correlated with bad emotions must be found. In a study on modulation of emotional response, participants were shown angry or frightened facial expressions while their brain activity was measured using fMRI (Hariri, Bookheimer, & Mazziotta, 2000). The results showed that neocortical networks of the limbic system were active during the stimulus presentation. More specifically, the activity of the amygdala in both hemispheres validate their role as the brain's fear. The amygdala does not only play a critical role in fear conditioning, but it is implicated in negative affectivity and pathophysiology such as anxiety disorder (Cannistraro & Rauch, 2002; Rauch, Shin, & Wright, 2003). In their review about the role of the amygdala in humans, Davis & Whalen (2001) confirmed the role of the

amygdala in fear and negative emotions by stating that "a stimulus that predicts an aversive outcome will change neural transmission in the amygdala to produce the somatic, autonomic and endocrine signs of fear, as well as increased attention to that stimulus". Next to the amygdala, the role of the anterior cingulate cortex (ACC), another area of the limbic system, was also found to contribute to negative affect and pain (Shackman et al., 2011). Finally, a brain area which is not part of the limbic system, but it is often correlated with negative emotion regulation, is the insula, a portion of the ventrolateral prefrontal cortex folded deep within the lateral sulcus (Augustine, 1996). In 2004, a study demonstrated that higher amount of grey matter in the right anterior insular cortex was correlated with negative emotional experience (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Thus, the major three main areas that have been the main target for negative affectivity are the amygdala, the ACC, and the insular cortex.

Neurofeedback and emotional regulation

Even though the areas which are most related to negative emotions were found and largely studied, this location is not absolute and each person might show differences because of a different shape or a different size of the brain (Brett, Johnsrude, & Owen, 2002). The consequences of these individual differences are that ROIs need to be identified independently for each participant in each rtfMRI neurofeedback study. Only when this data is available can fMRI-neurofeedback be used to train participants to downregulate the areas in the cortex that are associated with processing negative stimuli (Sulzer et al., 2013). There is already a lot of research showing that brain networks associated with negative affectivity can be regulated using neurofeedback.

In one of these studies, the success of rtfMRI neurofeedback in regulating amygdala activation was confirmed (Paret et al., 2014). The researchers included two groups taken from a healthy women sample: an experimental group who received activation feedback from the amygdala, and a control group that received feedback from a control region in the basal ganglia. Subjects in both groups were asked to down-regulate the activity in the amygdala in response to aversive pictures. Participants receiving amygdala feedback learned to down-regulate amygdala activation. This ability was maintained over time even in absence of the feedback signal, which confirmed the long-lasting effects of neurofeedback training. The authors also suggested that feedback from the control region is not helpful in down-regulating amygdala activation. These results demonstrated that it is possible to control the amygdala responses to positive stimuli which are lessened in patients suffering from major depressive disorder

(MDD). While previous studies only investigated the right amygdala, the ability to regulate the activation in the left amygdala was studied in relation with Major Depressive Disorder. The authors found this ability to be a possible novel therapeutic approach in the treatment of the disorder (Young et al., 2014).

The amygdala is not the only region involved in processing negative affectivity. In 2010, a study individualized the amygdala and insula region in 13 participants who volunteered in a research on negative emotion regulation (S. J. Johnston, Boehm, Healy, Goebel, & Linden, 2010). During the neurofeedback sessions, subjects used different mental strategies to regulate the feedback over the thermometer image. Most participants were able to gain control of amygdala and insula in the first session. Activity in the precuneus and medial prefrontal cortex increased during upregulation of emotions. Furthermore, with increasing training success, the ventral striatum was also found to increase its activity. In another study, fifteen right-handed subjects all learned to regulate activity in the anterior insular (AI) in only three sessions of about four min each on the same day (Caria et al., 2007). In a subsequent session, participants were asked to regulate the same ROI (AI) without receiving the neurofeedback and they were still able to activate or deactivate the region using different strategies. This study demonstrated that one single-day training with rtfMRI neurofeedback is sufficient to reach control over brain areas.

Research provides evidence that emotion regulation is prospectively related to pain intensity (Paquet, Kergoat, & Dubé, 2005). In a famous study performed in 2005, participants deliberately controlled the activation in the rostral anterior cingulate cortex (rACC), a region that mediates the perception of pain in humans (Christopher deCharms et al., 2005). Moreover, the study revealed that the up and downregulation of the rACC was correlated with the perception of pain artificially induced by a noxious thermal stimulation. In addition, patients suffering from chronic pain were trained to control the neural activity in the rACC. Results showed that all the patients showed a reduction in chronic pain after the training.

Discussion

This review described how subjects can learn to regulate their negative emotional states by controlling the brain activation of related brain regions using Real-time fMRI techniques. After the advent of this technology, neuroscientists extensively analysed the brain to discover its functions, including areas involved in emotional processing. When negative emotions were induced to subjects, few regions in the limbic system and frontal cortex showed strong activation in the brain. More specifically, the insula cortex seems to regulate negative

affectivity, the amygdala processes information of fear and anxiety, and the anterior cingulate gyrus is involved in the perception of pain. These regions were taken into consideration by studies in cognitive neuroscience, which demonstrated that they can be regulated using rtfMRI. By reducing the neural activity in these locations, participants could lower feelings of unease, suggesting new ways for the treatment of psychopathological disorders such as anxiety and depression. It is important, however, to carefully evaluate the results of these studies. For example, in the study by Paret et al. (2014), the rostral part of the basal ganglia was used as control regions, which is part of a network called the limbic loop. This network is not only involved in the control of movement, but also in the regulation of emotions, motivation of behaviour, and mood changes (Alexander, DeLong, & Strick, 1986). For this reason, the rtfMRI neurofeedback in this area could influence activity in the amygdala thus indirectly influencing emotion regulation and invalidating the results. Nevertheless, the studies presented provided an overall satisfactory evidence that subjects can learn to self-regulate activity in brain areas associated with negative valence.

A different approach might be to up-regulate brain areas associated with positive emotions including higher sensory areas, paralimbic and orbitofrontal cortex (S. Johnston et al., 2011). However, this approach still requires more investigation. It was demonstrated that cognitive load is also capable to turn down the emotional brain (Van Dillen, Heslenfeld, & Koole, 2009). A further alternative that could be studied in the future would be trying to upregulate brain regions associated with cognitive load and investigate how it would affect mood and negative emotions.

In all these studies, subjects used both positive and negative mental imagery in order to regulate brain activation. Some of these positive strategies include recalling themselves playing music, playing with the offspring, recalling of holidays, or engaging in sports. Negative strategies mostly included anger states or dangerous situations. However, a limitation of these studies is that not everyone is capable of producing mental imagery. Thus, these results might not be applicable to all subjects.

A further limitation of these studies is that using fMRI scanners to regulate negative affectivity is relatively inaccessible to society because of costs and complexity of the process. Future research should focus on how to make this method more accessible. On this account, few studies showed promising results using functional Near-infrared spectroscopy (fNIRS), a spectroscopic method that uses the near-infrared region of the electromagnetic spectrum to localize brain activity. In one of these studies, participants learned to regulate emotions by

controlling activity in the dorsolateral prefrontal cortex (Sakatani, Takemoto, Tsujii, Yanagisawa, & Tsunashima, 2013).

Given the limitation, it is clear that further research is needed. Nevertheless, these studies suggests that rtfMRI can be a powerful therapeutic method to regulate negative affectivity in patients suffering from depression or other disorders related to negative emotions. The review described studies in which patients show a decrease in the magnitude of experienced negative emotions including sadness, anxiety, depression, and pain.

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