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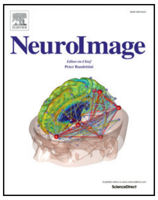

Voluntary control of anterior insula and its functional connections is feedback-independent and increases pain empathy

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ABSTRACT

Real-time functional magnetic resonance imaging (rtfMRI)-assisted neurofeedback (NF) training allows subjects to acquire volitional control over regional brain activity. Emerging evidence suggests its potential clinical utility as an effective non-invasive treatment approach in mental disorders. The therapeutic potential of rtfMRI-NF training depends critically upon whether: (1) acquired self-regulation produces functionally relevant changes at behavioral and brain network levels and (2) training effects can be maintained in the absence of feedback. To address these key questions, the present study combined rtfMRI-NF training for acquiring volitional anterior insula (AI) regulation with a sham-controlled between-subject design. The functional relevance of acquired AI control was assessed using both behavioral (pain empathy) and neural (activity, functional connectivity) indices. Maintenance of training effects in the absence of feedback was assessed two days later. During successful acquisition of volitional AI up-regulation subjects exhibited stronger empathic responses, increased AI-prefrontal coupling in circuits involved in learning and emotion regulation and increased resting state connectivity within AI-centered empathy networks. At follow-up both self-regulation and increased connectivity in empathy networks were fully maintained, although without further increases in empathy ratings. Overall these findings support the potential clinical application of rtfMRI-NF for inducing functionally relevant and lasting changes in emotional brain circuitry.

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Introduction

While functional magnetic resonance imaging (fMRI) has greatly advanced our understanding of the neurobiological basis of brain-based disorders, particularly psychiatric conditions, the clinical application of fMRI remains limited (Botteron et al., 2012). Recent developments in fMRI technologies have the potential to promote the translation of fMRI approaches from basic scientific research to clinical applications, including innovative and non-invasive treatments for psychiatric disorders (Linden, 2014; Stoeckel et al., 2014). One of the most promising technologies is real-time fMRI (rtfMRI), which allows real-time assessment of regional brain activity (see Weiskopf et al., 2003, 2004, 2007; Weiskopf, 2012 for a detailed overview).

rtfMRI is a powerful technique to transform the real-time activity of brain regions into visualized feedback, which enables subjects to learn volitional control over regional brain activity. To date this neurofeedback (NF) approach has been used in the context of a number of important nodes in cognitive and emotional processing networks, such as the inferior frontal gyrus (Rota et al., 2008), amygdala (Brühl et al., 2014; Paret et al., 2014; Posse et al., 2003; Zotev et al., 2011), anterior cingulate cortex (ACC; Weiskopf et al., 2003; deCharms et al., 2005), amygdala–insula networks (Johnston et al., 2010) and even the mesolimbic dopamine system (Sulzer et al., 2013). Importantly, initial clinical studies have also produced promising results, suggesting that rtfMRI-NF is a safe and efficient non-invasive strategy for helping to modify aberrant brain activity patterns in psychiatric populations (Hawkinson et al., 2012; Linden, 2014; Stoeckel et al., 2014), including patients with major depression (Linden et al., 2012; Young et al., 2014), contamination anxiety (Scheinost et al., 2013) and schizophrenia (Ruiz et al., 2013). Nevertheless, research has only just begun to explore the therapeutic application of rtfMRI-NF as a neuromodulatory strategy and several important issues need to be clarified (Linden, 2014; Stoeckel et al., 2014; Sulzer et al., 2013). As with other novel neuromodulatory treatment strategies, such as transcranial magnetic stimulation (TMS) (Rossi et al., 2009), the therapeutic potential of rtfMRI-NF particularly depends on: (1) whether the alterations in brain activity are of functional relevance (i.e. affect emotional or cognitive processing of the individual both in terms of behavior and alterations in functional circuitry in the brain), and (2) whether the neuromodulatory

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effects last beyond the duration of initial training in the absence of further feedback.

To specifically address these questions, we conducted a sham-controlled between-subject study that used rtfMRI-NF to train healthy subjects in the volitional control of the anterior insula (AI), and assessed neural (activity and functional connectivity) and behavioral indices of success during initial training and then subsequently their maintenance after 2 days in the absence of feedback. The AI insula is involved in a broad range of cognitive and social emotional functions which support successful social interaction and flexible behavioral control (Adolphs, 2003; Engen and Singer, 2013; Simmons et al., 2013; Koban and Pourtois, 2014). Previous studies indicate a crucial contribution of the AI in empathic processing (Decety and Jackson, 2006; Engen and Singer, 2013; Lamm et al., 2007; Singer, 2006). Particularly the empathic response during the observation of others suffering from pain (pain empathy) seems to specifically and crucially depend on the AI (Gu et al., 2010, 2012; Jackson et al., 2005, 2006; Lamm et al., 2011; Singer et al., 2004). Moreover, aberrant AI processing has been observed across the most common psychiatric disorders, including major depression (Hamilton et al., 2012), anxiety (Etkin and Wager, 2007) and autism spectrum disorders (ASD) (Di Martino et al., 2009) and initial studies have revealed deficient empathic processing in psychiatric disorders with social emotional deficits, such as ASD and schizophrenia (Derntl et al., 2009; Jones et al., 2010) that might contribute to the social interaction difficulties commonly observed in these patient populations. Given the highly specific role of the AI in pain empathy and its relevance for a range of psychiatric disorders, pain empathy ratings were chosen as a sensitive behavioral read-out to evaluate the functional relevance of the volitional AI regulation.

While previous studies have demonstrated successful AI modulation in healthy and psychiatric populations after brief rtfMRI-assisted NF training, reports of functional effects have been inconsistent (Caria et al., 2010; Veit et al., 2012; Berman et al., 2013; Lawrence et al., 2014; Ruiz et al., 2013). Thus one study found associations between successful modulation of AI activity and valence ratings (Caria et al., 2010), whereas others failed to (Berman et al., 2013; Lawrence et al., 2014). Valence processing is a continuous and partly implicit evaluative process that critically relies on additional brain regions, particularly the amygdala (Berntson et al., 2011). In contrast, pain empathy processing has been specifically associated with the AI (Lamm et al., 2011; Bernhardt and Singer, 2012) and particularly relates to pain observation in others. It seems reasonable to hypothesize therefore that pain empathy processing might have a higher sensitivity for demonstrating behavioral effects of a focal AI modulation using rtfMRI-NF.

Similarly, while some previous rtfMRI studies have suggested that subjects can maintain volitional control of their brain activity in the absence of NF (e.g., Scheinost et al., 2013; Young et al., 2014), others have not (Berman et al., 2013). However, assessments of training success have usually been made immediately after training without a strict control for non-specific training effects by using a sham group and only in terms of regional activation rather than functional indices (overview in Linden, 2014; Stoeckel et al., 2014). Furthermore, no studies have investigated the effects of learned volitional control of the AI on its patterns of functional connections during effective regulation or in terms of its resting state functional connectivity (RSFC).

The present study used a randomized double-blind sham-controlled between-subject design to evaluate the neurotherapeutic potential of rtfMRI-NF. Given that meta-analytic data indicates predominant left AI (LAI) activity during emotional processing and a previous reported altered valence rating after LAI rtfMRI-training, the LAI was chosen as the target ROI (Caria et al., 2010; Wager et al., 2003). Neural and behavioral effects (pain empathy ratings) of rtfMRI-NF training of the AI were assessed during the training and after two days without feedback being given. In line with previous studies (Hampson et al., 2011; Scheinost et al., 2013), resting state fMRI scans were included before and after the training to capture complex changes at the network level (see Fig. 1a for an overview).

Materials and methods

Participants

37 healthy students (19 male, mean age = 21.97 years, SD = 1.40) from the University of Electronic Science and Technology of China (UESTC) participated in the study. 21 subjects (10 male) were randomly assigned to the experimental group and 16 subjects (9 male) to the control group. All subjects gave informed consent before the experiment and were free of past or current psychiatric or neurological disorders. 3 subjects were excluded due to excessive head movement larger than 3 mm or 3 degrees (1 male in each group and 1 female in the control group). Another 2 subjects were excluded due to reporting being unable to perform the regulation strategies when debriefed after the whole experiment (2 females in the experimental group). In a post-scan interview these latter two subjects reported that they could not recall negative memories or felt nothing when recalling negative personal events. Thus 18 subjects in the experimental group and 14 subjects in the control group were included in the final analysis. To exclude potential confounding effects from personality traits or current mood states, all subjects completed the Chinese versions of validated psychometric questionnaires before the start of the experiment, including the Positive and Negative Affect Schedule (PANAS — Watson et al., 1988), Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS — Carver and White, 1994), Autism Spectrum Quotient (ASQ — Baron-Cohen et al., 2001), Beck Depression Inventory-II (BDI-II — Beck et al., 1996), State–Trait Anxiety Inventory (STAI — Spielberger et al., 1983), and Empathy Quotient (EQ — Baron-Cohen and Wheelwright, 2004). Written informed consent was provided to all subjects before study inclusion. The study and all procedures were approved by the local ethical committee at UESTC and were in accordance with the latest version of the Declaration of Helsinki.

Experimental group

fMRI localizer task

In line with previous rtfMRI-NF studies (Caria et al., 2010; Ruiz et al., 2013; Veit et al., 2012), the LAI was initially localized functionally for each subject. To this end subjects were presented with color pictures depicting individuals in painful situations and neutral pictures in a blocked design session. All painful pictures (mean valence 2.90 ± 1.15, mean arousal 5.07 ± 1.03) in the present study were from Meng et al. (2012). These pictures depicted painful situations that occasionally happen in daily life, such as a hand cut by a knife or stabbed by a syringe (see Fig. S1 for examples; Meng et al., 2012). All neutral pictures were from the International Affective Picture System (IAPS; Lang et al., 2005) and depicted neutral objects such as a book or a chair (mean valence 4.95 ± 0.15, mean arousal 2.77 ± 0.44). Subjects were instructed to imagine how painful the person feels when presented with a painful picture, and to just watch when presented with a neutral picture. The localizer consisted of 8 blocks (4 blocks of neutral pictures and 4 blocks of painful pictures) alternating with a 30 s baseline interval (fixation cross). Each picture was presented for 2 s and there were 10 pictures within each block. The pictures within each block were presented randomly to subjects. The localizer session lasted about 7 min.

NF training task

The NF training task was adopted from a procedure used by Caria et al. (2010) and consisted of 4 training sessions each lasting about 10 min. During each session, 5 regulation blocks (30 s) alternating with 6 baseline blocks (30 s) were presented. During NF training subjects in the experimental group viewed a display showing the activity within the LAI region of interest (ROI) as a graphical thermometer

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