Interoceptive Awareness and the Insula – Application of Neuroimaging Techniques in Psychotherapy

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Abstract—**Interoceptive awareness is defined as the awareness of stimuli originating inside one's own body such as the heartbeat. The emergence of new brain imaging techniques like functional magnetic resonance imaging (fMRI) or magnetic resonance spectroscopy (MRS) has increased our knowledge of neural substrates underlying interoceptive awareness. In particular, the bilateral brain structure of the insula has been identified as a key region involved in interoceptive processes in healthy populations. In line with prominent theories of human emotion, the insula has an important function in connecting interoceptive awareness with affective experience. This connection hinging on the insula between interoception and emotional processing is suggestive of an involvement of the insula in mood disorders such as major depressive disorder (MDD). Multilayered deficits in the insula cortex of depressed individuals such as abnormal function, biochemistry, and anatomy support this hypothesis.**

The aim of the present article is a) to describe the importance of the insula for the interplay between interoception and emotional processing and b) how this might be figured into psychotherapeutic treatment of depressed patients using new imaging techniques like real-time fMRI.

The article begins with a brief introduction about neuroanatomical settings of the insula (I. Introduction–Neuroanatomical background of the insula). Afterwards, early behavioral studies to investigate interoceptive awareness are described (II. A step Back–First attempts to investigate interoceptive awareness), followed by a description of more recent imaging studies outlining neural mechanisms underlying interoceptive awareness and emotional processing in the insula (III. The insula as key region involved in functional interoception and emotion.) Throughout, the article addresses the question of why the investigation of individuals suffering from depression might provide novel insights into the neural underpinnings of interoceptive awareness and its link to abnormal behavior (IV. Why study interoceptive awareness in depressed participants?).

Following the description of a selected study that combines for the first time functional results of interoception (using fMRI) with biochemical results of the insula (using MRS) (V. Neuroimaging in interoceptive awareness combining fMRI and MRS – A specific study), the article concludes with a perspective outlining the potential for using imaging techniques like real-time fMRI to enhance neural activity in the insula during interoceptive awareness. This approach potentially leads to faster recovery in depressed patients and might be the first therapeutic application of functional imaging in psychiatry (VI. Perspectives: Neurofeedback in major depression using real-time fMRI).

Keywords: interoceptive awareness; insula; major depression; emotional processing; functional magnetic resonance imaging

I. Introduction–Neuroanatomical background of the insula

The insula is located within the Sylvian fissure of each hemisphere and is an important structure involved in the processing of the physiological condition of the human body, which is termed interoception [1–3] . This construct was originally restricted to sensations solely from the viscera [4] . It has been broadened to a generalized sensory capacity basing on a phylogenetically novel ascending interoceptive pathway in primates. This so-called lamina I spinothalamocortical pathway from the body to the cortex (including the insula) is the neuroanatomical substrate that enables an interoceptive cortical representation of the body [1,3] . In more detail, two parallel pathways project via brainstem nuclei to distinct thalamo-cortical relay nuclei, which in turn project to posterior parts of the insula cortex [1–3] . One pathway contains sympathetic and the other parasympathetic information from small-diameter afferents. According to Craig, interoceptive information is gradually processed in the insula, beginning in the posterior part of the insula, continuing to the middle part, and ending in the anterior part. Consequently, specifically the anterior insula is seen to play an important role in human awareness and particularly in interoceptive awareness.

In addition to connections with the insula, ascending projections of lamina I neurons also form a thalamocortical pathway in primates that innervates the anterior cingulate cortex [3] , a brain structure located along the cortical midline of the human brain and involved in a variety of functions such as emotional processing [e.g., 5] alongside its activation by autonomic functions. Additionally, both structures, the anterior insula and the anterior cingulate cortex, are often seen to be functionally co-activated in imaging studies dealing with emotions, suggesting an involvement of both structures in human emotional processing.

Alongside neuroanatomical findings, the emergence of new imaging techniques like functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetic resonance spectroscopy (MRS) have allowed active in vivo studies of interoceptive awareness. After presenting early efforts exploring the interplay between interoception and

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emotional processes, several important fMRI studies will be presented.

II. A STEP BACK–FIRST ATTEMPTS TO INVESTIGATE INTEROCEPTIVE AWARENESS

One of the most well known theories regarding the association between the body and emotions can be traced back to W. James and C. Lange. They stated, independently of each other, that in humans the perception of bodily signals is associated with the processing of emotional stimuli. James was one of the first to describe that an emotional stimulus has the capability to generate somatic changes, such as increasing the heart rate. The perception of these somatic changes in turn was seen by him as essential to the process of emotional experience. Their complementary ideas were combined in what is known as the James-Lange theory of emotion, a classical construct of the late 19th century.

Importantly, this theory, whilst having little experimental support at the time, served as a focus of debate on the topic, and hence stimulated research into bodily processes and their influence on emotional experience [6,7] .

In the course of criticizing existing theories of emotion and providing improved hypotheses (e. g. the Cannon-Bard theory [8] or the Schachter-Singer theory [9]), early experiments, still limited to investigations on the behavioral level, tried to provide new insights into the connection between bodily signals and emotional processing. In this context, Stuart Valins conducted an interesting early study in 1966 [10], showing that an auditory false heart-rate feedback influenced participants' judgment of emotional pictures. The study not only showed that physiological reactions have the capability of influencing emotional perception, but also had the potential to generate considerable ideas regarding the significance of that finding to emotional disorders in clinical psychology.

This aspect was later taken up by Schandry, who, similarly to Valins, utilized the heartbeat as an instrument for investigating bodily processes. While acquiring more sophisticated data about heart rate, respiration and skin conductance, he asked healthy participants to count their own heartbeat by focusing only on their internal bodily state [11] . The results of the experiment suggested that interoceptive awareness, the awareness of stimuli originating inside the body, is associated with behavioral scores of anxiety and emotional lability. In particular, higher accuracy in heartbeat perception was accompanied with higher scores of anxiety, suggesting again a link to psychiatric disorders.

The described concept of the embodiment of emotions has continued to be a widely discussed topic. Consequently, it is not surprising that further investigations and the development of theories have been pushed forward by the emergence of new brain imaging techniques. These methods have contributed significantly to enlightening neural and biochemical processes underlying awareness of one's own body and its relationship to the environment, as well as the interplay of that with emotional processing.

III. THE INSULA AS KEY REGION INVOLVED IN FUNCTIONAL INTEROCEPTION AND EMOTION

The first study using fMRI to investigate neural activity during interoceptive awareness was conducted in 2004 by Critchley and colleagues [12]. Similar to the work described above by Schandry, a heartbeat detection task was used to induce interoceptive awareness in healthy participants while in an MRI machine. During interoceptive experimental conditions, participants had to concentrate on their own heartbeat and judge if it was in sync with an externally applied tone. In exteroceptive conditions, participants had to concentrate on an externally applied tone and judge if one was played with a different pitch compared to the others. In addition, anxiety was measured outside the scanner purely at the behavioral level, a procedure comparable to Schandry's.

Critchley and colleagues [12], showed that interoceptive awareness is accompanied by increased neural activity in several brain regions like the insula. In addition, anxiety scores were correlated with neural activity in the insula. Since psychiatric conditions are often accompanied by somatic symptoms and increased attention to one's own body, this study supports the James-Lange theory of emotion and the hypothetical relationship between interoceptive awareness and emotional processes at the level of neural activity. It underlines the significance of the insula as an important node for mediating bodily awareness and emotional processing, specifically for psychiatric disorders. It can be hypothesized that the interaction of interoceptive awareness, emotional processing, and insula activity is abnormally modulated in psychiatric disorders.

Further imaging studies investigating neural activity in the insula during interoceptive awareness have supported and extended the findings of Critchley and colleagues. A recent fMRI study by Zaki and colleagues [13] showed for the first time that neural activity during emotional processing and interoceptive awareness overlaps in the region of the insula cortex. In their design they combined two different tasks in fMRI: during the emotional task participants watched and rated videos of other people describing emotional events. During the interoceptive task participants had to concentrate either on their own heartbeat or on an externally applied tone. They were instructed to tap with their finger either to the beat of their own heart, to the tone, or to the heartbeat while the tone was presented. This setup allowed investigation of whether structures involved in interoceptive awareness were also involved during emotional processing. Based on participant´s emotional ratings the authors were also able to investigate a relationship between emotional intensity and neural activity in regions involved in interoception. Confirming prior research, Zaki and colleagues showed that the interoceptive task enhanced neural activity in the insula. Interestingly, this pattern of neural activity was also engaged when participants rated the intensity of their emotional experience. The authors speak of a "convergence zone for representations of the body and emotion" [13, p. 498]. These results provide further evidence about the interrelationship between bodily awareness and emotional processing in the insula cortex.

Studies using functional connectivity, where patterns of intrinsic activity are correlated over time, have provided further details about the structure of the insula cortex. Several imaging studies have revealed a threefold regional organization within the insula [14,15]. In particular, the results of Deen and colleagues [15] suggest linked but dissociable networks across regions of the anterior insula and the cingulate cortex, specifically a dorsal network associated with cognitive control and a ventral network associated with emotional experience. A third functional connectivity network includes the posterior insula along with primary and secondary motor and somatosensory cortices. These results highlight the multimodal character of the insula and in particular its connection to anterior cortical midline structures, implying a potential role in emotional processes.

IV. Why study interoceptive awareness in depressed participants?

An ideal study population to further investigate the relationships between interoceptive awareness and emotional processing is, alongside healthy participants, individuals suffering from psychiatric disorders like major depression. The study of mental disorders allows exploring the underlying impaired brain activity during interoceptive awareness and emotional processing and correlating it to altered behavior. By comparison to healthy participants in terms of neural activity and behavioral values, conclusions can be drawn about impaired brain activity in depressed patients and how it might be associated with symptoms. These studies can serve to enlighten neural underpinnings of psychiatric disorders like depression and can lead to the development of more advanced treatment on the biochemical as well the behavioral level. Specifically, brain regions that show abnormal activity during interoceptive awareness might serve as target regions for treating affective disorders due to their association with emotional processing.

Affective disorders like major depression are of particular interest for investigating an interaction between interoceptive awareness and abnormal emotional experience since these patients show abnormalities in both domains on the behavioral as well as neural levels. Patients suffering from major depressive disorder (MDD), one of the leading causes of disability worldwide [16,17] , show impaired emotional processing, which includes feelings of hopelessness and guilt, loss of awareness of one's own feelings, and over-attribution of negative stimuli to one's own person, including the body [18–22] .

In addition, MDD patients often suffer from diffuse and persisting physical comorbidities. Typically these include headache, sensibility deficits in chest and abdomen, and increased muscle tension. These somatic symptoms go along with altered awareness of bodily symptoms as well as altered awareness of external stimuli [21,23,24] , which has been described as decreased environment focus and increased self-focus in MDD [18,25–27]. At the same time the accuracy of interoceptive heartbeat perception seems to be impaired in MDD [28], which can be seen as a result of impaired cognitive and decision-making functions. These deficits in MDD—on the one hand emotional and on the other hand interoceptive—present an interesting combination to target for further experimental studies.

Patients suffering from MDD are also characterized by reduced grey matter volume in the insula [29] as well as deficits at the biochemical level of receptors and neurotransmitters [30–34]. This provides another interesting point for the study of underlying abnormalities in major depression, in particular targeting the GABAergic deficit hypotheses of depression [31,34–37] . This posits a central role of deficient GABAergic transmission in the etiology of MDD. Supporting this hypothesis, several imaging studies in humans have shown decreased concentrations of this common inhibitory neurotransmitter (γ-aminobutyric acid) in depression, as well as the normalizing GABAergic transmission effects of antidepressant drugs. These deficits in depression can serve as a valuable hypothesis generator as the systems seen to be dysfunctional in MDD are likely to be those involved in healthy participants also. It can be hypothesized that deficits in depressed patients at the biochemical level, specifically GABA, are correlated with neural deficits during interoceptive awareness, specifically in the insula. However, the biochemical underpinnings of interoceptive awareness remain to be investigated in healthy participants (see below).

V. Neuroimaging in interoceptive awareness combining fMRI and MRS – A specific study

Targeting the question formulated above regarding the biochemical underpinnings of interoceptive awareness in the insula in healthy participants, Wiebking et al. [38] conducted the first study combining fMRI during interoceptive awareness and MRS in the insula. To ensure the reproducibility of neuroimaging studies and in line with good practice, a well-established paradigm in fMRI was used as introduced by Critchley and Pollatos [12,39] .

In this paradigm participants had to either silently count their own heartbeat (interoceptive condition), count an externally applied tone (exteroceptive condition), or simply rest. Trials of the three conditions were presented in pseudo-randomised order for 6–10 s. Simple visual stimuli were presented on the screen to indicate the condition: for the interoceptive condition a black heart on grey background was presented, for the exteroceptive condition a black musical note was presented, and for the rest condition a black fixation cross. As long as a symbol was visible on the screen, the subjects were asked to execute the specific task. After each counting phase the participants were asked to report the number of counted tones via button press. The presentation frequency of the tones was adapted to correspond to each subject's pulse-rate, which was read off from the online value of the Siemens Physiological Monitoring Unit. The onset time of the tones was jittered by 200 ms to avoid habituation effects. Any manipulation of the interoceptive task like holding the breath was not allowed and controlled by recording the participant's breathing intensity. In order to make the difficulty of the IA and the EA tasks comparable, tones were presented at an individually determined volume. To ensure equivalent difficulty of both tasks, participants were instructed to adjust the volume of the tone to the same perception difficulty level as that of counting their own heartbeat. This was done via a visual analogue scale at the beginning of the scan, i.e., with the scanner acquiring images to account for scanner noise.

Twenty-eight right-handed healthy participants (10 females, mean age 22.37 years ± 3.77 SD, 18–34 years) underwent fMRI and 27 out of this group participated in MRS scanning (10 females, 22.37 ± 3.85 years, days between scans 3.7 ± 2.7). Four participants were excluded due to anatomical abnormalities or motion artefacts (≥ 2 mm), culminating in 24 datasets for fMRI analysis (n = 24 participants, 9 females, 22.71 ± 3.95 years). All participants were questioned about psychiatric, neurological, or other diseases. Participants were recruited from the McGill University (Montréal) student body and the local community. The study was approved by the local ethics committee. All participants gave their written informed consent and were financially compensated. To ensure quality of the MRS data, only results with Cramer–Rao lower bounds (CRLB) ≤ 20% were included in the analyses. For further details of fMRI and MRS scanning parameters, please refer to the original publication [38].

To examine neural activity during interoceptive awareness, the interoceptive condition was contrasted with the exteroceptive condition. Confirming other studies using similar designs in fMRI, the neural activity in the insula during interoceptive awareness was significantly greater than in the exteroceptive condition. In addition, these results were confirmed by an independent study of thirty healthy subjects using the same fMRI paradigm. Although this approach—demonstrating consistent results across independent studies using the same task—is currently difficult to realize in fMRI research (due to the current cost of scanning), it is an excellent way to ensure high quality and reproducibility.

Using MRS, the concentrations of neurotransmitters like GABA and glutamate were determined. Prior studies demonstrated the sensitivity of MRS to detect decreases in GABA, for example after interventions such as learning [53] or transcranial direct current stimulation (tDCS) [54].

Concentrations were measured in two regions: the left insula cortex as the main region of interest and the mPFC (medial prefrontal cortex) as a control region. Neural activity during intero- versus exteroceptive awareness in the insula and mPFC was then correlated with the biochemical values in the respective region. Activity during interoceptive awareness in the insula positively correlated with GABA concentration in this region. No relationship was observed in the insula when comparing GABA to neural activity during exteroception nor when comparing interoceptive activity to other biochemical values like glutamate. Interestingly, while GABA and glutamate correlated positively with each other in both regions which might lead one to expect a similar impact for both, only GABA showed a statistically relevant relationship to interoception. Correlations in the mPFC region revealed a negative relationship between GABA and exteroceptive awareness. These findings provide evidence that the inhibitory neurotransmitter GABA is a key factor in the differential processing of intero- and exteroceptive awareness.

Considering a hypothetical involvement of the insula in depression, the authors integrated the Beck Hopelessness Scale (BHS), a behavioral measure for depression. GABA values in the insula correlated negatively with BHS scores—that is, higher depression scores were associated with lower GABA concentrations, which would go along the lines of the GABA deficit hypotheses of depression. More interestingly, neural activity in the insula during interoception also correlated negatively with depression scores. Although results were established in a healthy population and need to be investigated in a depressed population, this finding suggests that patients suffering from depression would show lowered neural activity during interoception in the insula.

In conclusion, the study by Wiebking and colleagues [38] showed that the concentration of GABA in the left insula is associated with neural activity during interoceptive awareness. Important findings were made for the generation of hypotheses regarding major depression. Depressed affect was related to both GABA values as well as neural activity during interoception in the insula. Since depression is characterized by a common pathophysiological pattern of GABAergic deficits [32,34,40,41] and altered states of internal and external awareness [18,25,42] , it would be of high interest to target these points in future research about interoception and depression to provide further evidence for a connection between these factors.

V. PERSPECTIVES: NEUROFEEDBACK IN MAJOR DEPRESSION USING REAL-TIME FMRI

The imaging studies described above show a certain pattern of brain activity during interoceptive awareness: enhanced neural activity during interoceptive awareness in the insula of healthy participants, reduced neural activity in the insula in participants suffering from major depression, and the association of neural activity with GABA during interoceptive awareness. These findings provide motives for the development of behavioral therapies in depression other than antidepressant treatment to normalize GABAergic transmission.

In line with cognitive behavioral therapy approaches to provide more efficient self-management skills for depression, relevant patterns of neural activation can be targeted in an imaging approach using fMRI-based neurofeedback. This new technique is a promising tool for the treatment of MDD and psychiatric disorders in general [43] . fMRI-based neurofeedback is realized as visual feedback of real-time changes in neural activity in a relevant brain region such as the insula via a screen that is mounted on the headcoil of the scanner (a setup comparable to that of many fMRI studies). In contrast to standard fMRI studies, the neural signal of the particular region must be processed in real time outside the MRI machine, leading to the label real-time fMRI (rtfMRI). Such real-time feedback allows the participant to practice specific cognitive strategies to control their mental state in explicit terms of neural markers, for example by learning to directly up- or down-regulate the measure of regional activity they are seeing. In order to make feedback more comprehensible and effective for the participant, it can be displayed in an intuitive format, such as by growing or shrinking bars as illustrated in Figure 1.

Neurofeedback through rtfMRI has several potential advantages. It combines the principles of cognitive-behavioral therapy with physical brain stimulation such as transcranial magnetic stimulation (TMS). Moreover, the immediate character of the feedback in terms of real-time brain activity can play an important role for depressed patients in particular since they often show a lack of motivation.

Several studies using rtfMRI were able to show that self-regulation by certain cognitive strategies of neural activity in several brain regions like the somatomotor cortex [44,45] and anterior cingulate cortex [46,47] is possible. Interestingly, Caria and colleagues [48] were able to show that self-regulation of the anterior insula during rtfMRI is possible, at least in healthy participants. Since pilot data showed that participants needed instructions for mental strategies to gain control over this area, they suggested them to recall emotional events. Indeed, all participants were then able to successfully regulate their brain activity in the anterior insula. As discussed in the paper, these results can be seen in light of increased interoceptive awareness during subjective emotional responses. Whether depressed patients are also able to modulate insula activity and whether these newly acquired cognitive skills may endure and lead to improvement of mental well-being is a hypothetical construct that has been tested in first exploratory steps.

Importantly, a recent study by Linden [43] investigated the effects of rtfMRI also in a group of depressed patients. Their participants learned during four neurofeedback sessions to increase brain activity in regions involved in the generation of positive emotions like the insula cortex. The authors showed that neurofeedback leads to faster improvement of depressive symptoms as compared to a control group that practiced the same cognitive strategy without rtfMRI. These results suggest that skills acquired by rtfMRI can be more effective than gaining control of physiological functions of the peripheral nervous system such as the ability to influence the heart rate via ECG biofeedback (electrocardiogram). The activity of the brain is central for generating behavior and the integration and coordination of processes in the peripheral nervous system. Hence, physiological processes like the heart rate or mental processes like depressive ruminating thoughts can be targeted much more effective through neurofeedback directly at their core, i.e. activity of the brain. Taking together findings in rtfMRI studies and the previously described results of studies of interoception in fMRI, one might be able to formulate an effective interoception/insula-based rtfMRI approach for use in depression (see Figure 1). In order to enhance neural activity in the insula, depressed patients could start by practicing a heartbeat counting task outside the scanner (Figure 1, left upper corner). This cognitive strategy could then be used during rtfMRI sessions, where patients should learn through positive/negative neurofeedback to voluntarily influence the activity of the insula region (Figure 1, right lower corner). The above-mentioned rtfMRI study by Linden et al. [43] showed an improvement of control of neural insula activity over scanning sessions. Here, depressed patients had to mentally engage in positive imagery strategies to generate positive emotions. However, it might be difficult for depressed patients later in everyday life to mentally engage in positive situations, especially without the experience of actual neural feedback as shown in this study [43]. Hence, the approach to use interoceptive awareness in everyday life might be more effective and naturalistic compared to mentally engage in positive emotions. In addition, an fMRI study conducted by Farb and colleagues [49] showed increased neural activity in the insula after mindfulness-based training. This training has been shown to have benefits on several levels [e.g., 50–52] , suggesting that greater awareness of mental processes in this way can have an antidepressant and overall positive effect on an individual's well-being. Since local communities often offer such programs, it might be easier for depressed patients to maintain and practice acquired interoceptive strategies during rtfMRI (Figure 1, left lower corner). However, this approach has potential to be a possible first therapeutic application of functional imaging in the area of mental health research.

VI. CONCLUSION

Research that mainly using fMRI in combination with heartbeat counting paradigms in healthy participants has showed that brain activity during interoceptive awareness is strongly associated with the insula. At the same time, neural activity during emotional processing co-occurs and is influenced by interoceptive awareness. This connection of interoception and emotions makes their joint study in the context of major depression particularly intriguing. Here, deficits can be seen on several levels, including the emotional as well as the biochemical. Advancing knowledge of biochemical underpinnings of interoceptive awareness in the insula support a triangular relationship between biochemistry, depression, and interoceptive awareness in this region.

Further development in the area of neuroimaging technology makes it possible to target these arguments in depressed patients, which might lead to the development of more sophisticated cognitive behavioral therapy approaches. Neurofeedback through real-time fMRI bears the potential to be the first therapeutic application of functional imaging in the area of mental health.

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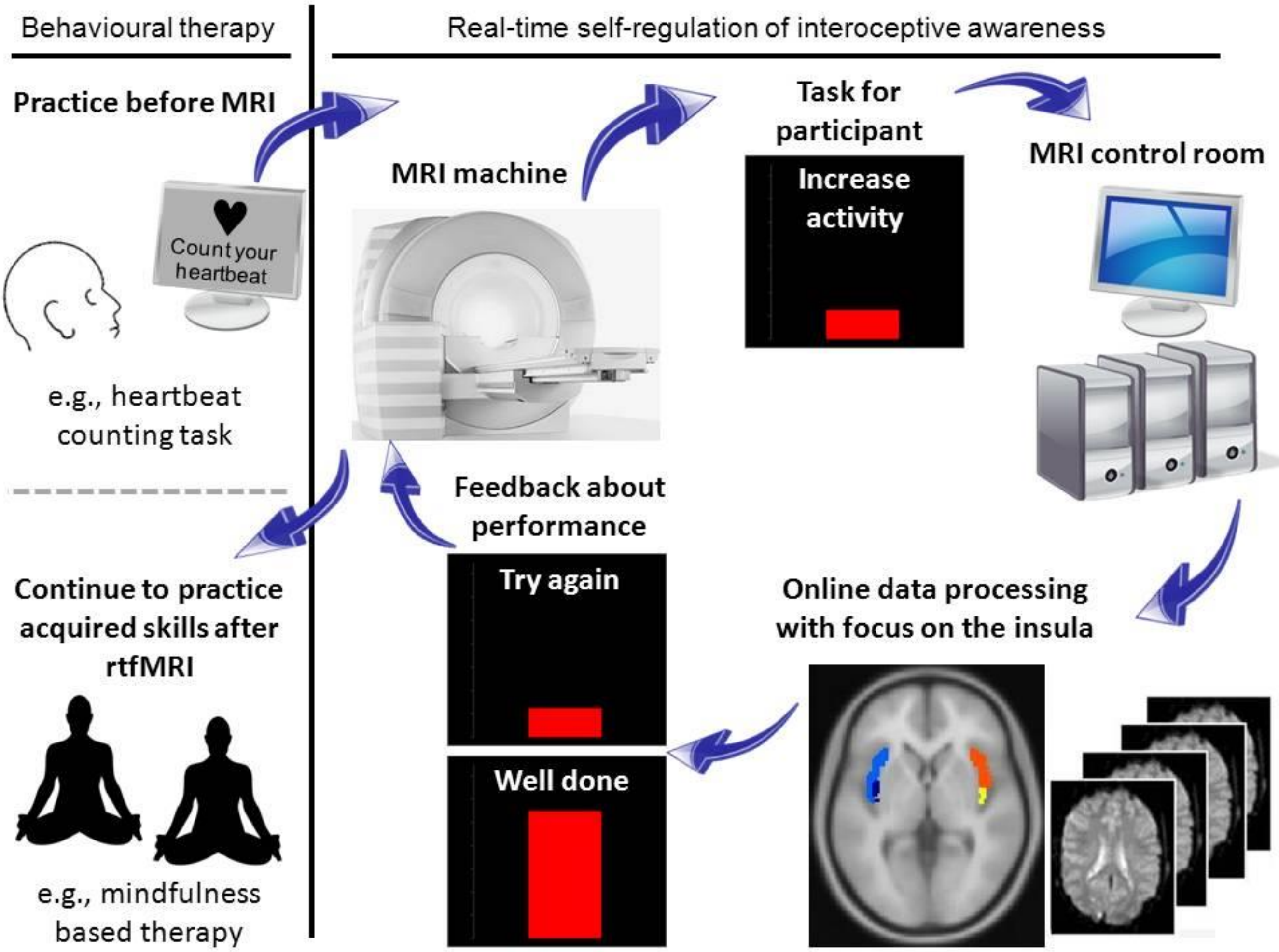

Figure 1: Neurofeedback during rtfMRI. Image prepared by CW.

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