Creating a new tool for Post-Traumatic Disorder treatment:
Real-time functional magnetic resonance imaging neurofeedback of rostral anterior cingulate cortex

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Dissertation at the
Graduate School of Systemic Neurosciences
Ludwig-Maximilians-Universität München

July 2019

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Date of Submission:	**23 July 2019**
Date of Defense:	**16 March 2020**

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Summary

The first article on real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback was published in 2003 (Weiskopf et al., 2003) with the aim to enable the subject to learn to control activation in rostral-ventral and dorsal anterior cingulate cortex (ACC). Rt-fMRI neurofeedback involves data collection of neural activity, real-time data preprocessing, online statistical analysis, providing the results back to the participant, and active effort of participant in order to either up- and/or down-regulate the target region's activation. In the last 16 years the topic attracted great attention from different labs around the world and many different brain regions were regulated with the help of rt-fMRI neurofeedback. Nevertheless it had the most distinct impact in the clinical research as it could be used with clinical population in order to normalize their abnormal neural activity. The dissertation focused on the implementation of the rt-fMRI neurofeedback to the Post-Traumatic Stress Disorder (PTSD) patients.

PTSD is developed as a result of experiencing a traumatic event in first hand or hearing that a close one experienced it. PTSD has a high prevalence (Kessler et al., 2005) and also high impact on the patient's life quality (Warshaw et al., 1993). Unfortunately the response rate to the therapy is around 50% (Bradley et al., 2005; Stein et al., 2006). Hence, there is a need for a new treatment tool for PTSD. The neurocircuitry model of PTSD indicate that there is increased activity in amygdala, decreased activity in ventromedial prefrontral cortex (vmPFC)/rostral ACC (rACC) and hippocampus (Rauch et al., 2006). Animal model of PTSD revealed that stimulating rACC led to increase in extinction learning and rats exhibited less PTSD symptoms (Milad &

Quirk, 2002). Following these findings, we decided to implement rACC rt-fMRI neurofeedback to PTSD patients.

The first study focused to develop a new paradigm to target rACC and tested it with healthy population. We used Ekman faces as functional localizer in order to locate the rACC. Experimental design constituted of four functional runs in one session. The main aim was to assess the methods effectiveness in one session. Surprisingly eight out of sixteen female participants learned to regulate their rACC, whereas only four out of sixteen male participants were able to regulate their rACC at will. Interestingly the learner/non-learners are not widely reported in the rt-fMRI literature and no gender difference has been reported so far. As a result we decided to implement it with only one sex in PTSD group.

In the second study we tested the paradigm with the female PTSD patients. Eight out of sixteen PTSD patients gained control over their rACC. We also found that PTSD patients recruited more brain regions, especially multi-sensory brain regions for the upregulation of rACC in comparison to healthy subjects. We failed to find a single factor to predict rACC control success across groups. There is a need for further study to identify the predictor factors.

As a result we concluded that the best practice of rt-fMRI with PTSD patients would be to use it as a supportive tool to psychotherapy in order to identify the best working strategy for their treatment. Further research recommendations are discussed below.

1. Introduction

Everyday human kind makes some more progress in technology and with this accumulating knowledge we are inspired limitlessly. Developments in the neuroimaging are one of these fields, where every single day the number of published articles is growing and acquired knowledge is used to improve our lives. The first functional magnetic resonance imaging (fMRI) article was published in 1990 (Ogawa et al., 1990) and in only 13 years we made the progress to be able to analyze the data in real time and to feedback the activation related data to the subject who is lying in the scanner (Weiskopf et al., 2003). After the first real-time functional magnetic resonance imaging (rt-fMRI), the topic drew attention in the clinical research.

The purpose of the studies presented in this thesis was to identify a new tool for post-traumatic stress disorder (PTSD) treatment. The first project focused to establish a new paradigm to upregulate the rostral anterior cingulate cortex (rACC) and to test it with healthy population. The second project aimed to implement the paradigm with PTSD patients.

In the following chapters, there will be an overview of neurofeedback with a focus on rt-fMRI neurofeedback. Furthermore, PTSD will be discussed regarding the underlying neural abnormalities in order to justify the need for a tool to normalize PTSD patients' neural activity.

1.1. Neurofeedback

Behaviorism had a huge impact on psychology science in the mid 20th century. Learning results directly in a behavioral response; hence everything is learned and can be learned (Chiesa, 1994). Biofeedback has emerged in this environment. It is a methodology, which directly measures subject's physiological state and feed this information back to be modulated in order to raise awareness about the process and to acquire voluntary control over the body. The underlying process is explained as operant conditioning / instrumental learning (Skinner,

1938; Christopher deCharms et al., 2004; Weiskopf et al., 2004; Sitaram et al., 2016). Thorndike (1901) has observed that behaviors resulting in satisfying consequences are strengthened and behaviors resulting in unsatisfying consequences are weakened. In the context of biofeedback, the subject observes the feedback about the physiological measurement and tries to modulate it by using a strategy. In case the strategy is successful, then it is likely to be strengthened and in case it is not successful, the subject would change the strategy. Subjects learn to modulate related physiological responses as a result of contingent feedback or reward (Fetz, 2007). They do not need the signal itself, receiving a reward such as money as a result of successful modulation will also encourage learning.

First reported gained volitional control over physiological response during biofeedback was reported in 1968 (Kamiya, 2011). After the implementation of biofeedback of neural activity, the field grew very quickly aiming to improve performance or for clinical purposes. Biofeedback is used for different physiological measurements, such as muscle activity measured by electromyography to treat headaches (Haynes et al., 1975), skin temperature measured by thermistor to treat Raynaud's Disease (Keefe et al., 1980), galvanic skin response measured by electrodes to treat epilepsy (Nagai et al., 2004), respiration measured by thermistor to treat Attention Deficit Hyperactivity Disorder (ADHD) (Sonne & Jensen, 2016), heart rate variability measured by electrocardiogram to treat depression (Karavidas et al., 2007), and neural activity measured by electroencephalogram (EEG) to enhance the performance of musicians (Gruzelier et al., 2014).

Neurofeedback is a type of biofeedback using neural activity as its source of physiological activity. There are subtypes of neurofeedback classified by the measurement method. Electrophysiological methods measure the electrical activity of the brain. So far subjects have

been able to regulate their brain activity by using EEG (Kamiya, 2011), magnetoencephalography (MEG) (Okazaki et al., 2015), and invasive electrocorticography (ECoG) (Gharabaghi et al., 2014). Another technique to measure neural activity is haemodynamic imaging methods (Logothetis et al 2001). Functional near-infrared spectroscopy (fNIRS) (Saita et al., 2018) and realt-time fMRI (rt-fMRI) are the common methods for haemodynamic response focused neurofeedback.

Most commonly used neurofeedback methods are EEG and rt-fMRI. EEG neurofeedback has been implemented first in the 1960s (Kamiya, 2011) and since then it is widely used to improve knowledge about brain mechanisms and cognition and/or behavior, to train cognitive performance (also known as peak-performance training), and to normalize patient's brain activity (Enriquez-Geppert et al., 2017). Because it is available over 50 years now, there are different well-established methodologies for EEG neurofeedback such as frequency, deep-state, and synchrony training (Orndorff-Plunkett et al., 2017). Even though EEG is a cheap methodology, it requires many sessions to gain control over the brain activation. As a result it might lead to high drop out ratios. In comparison to EEG neurofeedback, rt-fMRI neurofeedback is more expensive, however it is easier to learn to modulate brain activity (Birbaumer et al., 2013). This easiness of learning is attributed to the fact that brain monitors the vascular system and rt-fMRI relies on blood-oxygen-level-dependent (BOLD) signal, nevertheless human brain is incapable of processing neuroelectric signals, which is the target of EEG neurofeedback. Based on the brain's receptors, Birbaumer and colleagues (2013) argued that rt-fMRI neurofeedback enables faster 'sharpening' of the response. Additionally, EEG signal has inherently inverse problem because it is a result of activity of 6 million neurons in the brain, which means poor spatial source localization (deCharms, 2008). In comparison, rt-fMRI has a very high spatial

resolution in millimeters enabling participants to learn to modulate specific brain regions. There is one more differentiating factor between EEG and rt-fMRI signal that is time resolution. EEG signal can be measured and feedback almost in real time, however BOLD signal peaks around 4 seconds later after the initial brain activation (Logothetis et al., 2001). Overall, EEG and rt-fMRI neurofeedback have different pros and cons and they are suitable to answer different sets of questions.

1.1.1. Development of rt-fMRI

The first published fMRI study dates back to 1990 (Ogawa et al., 1990) and the first published rt-fMRI neurofeedback article dates back to 2003 (Weiskopf et al., 2003). During 13 years between these two studies, a series of developments led to the feasibility of rt-fMRI neurofeedback.

First crucial step was the statistical calculations; hence fMRI data processing relies heavily on statistics in order to exclude the noise. Cox and colleagues have reported first near real-time analysis of fMRI in 1995. Even though it was a break through, preprocessing steps were missing. In the following years the preprocessing steps such as 3D motion correction (Cox & Jesmanowicz, 1999), temporal filtering, spatial smoothing (Posse et al., 2003), and spatial normalization (Gao & Posse, 2003) were achieved to be carried out in real time as well. Nowadays the real-time preprocessing is nearly as good as offline preprocessing (Weiskopf, 2011). Additionally, discovery of multi-echo EPI resulted in faster imaging sequence and maximized BOLD sensitivity (Posse et al., 1999; Feinberg et al., 2010).

Furthermore, rt-fMRI neurofeedback benefited from statistical and analysis developments. Voyvodic (1999) advanced t-test for real-time analysis of fMRI data. Correlation

analysis (Posse et al., 2001) and General Linear Model (GLM) (Goebel, 2001) became available consecutively. The advancement of support vector machine in real-time (LaConte et al., 2007) derived a new field.

After the advancement of rt-fmri, software such as Turbo Brain Voyager (TBV - Brain Innovation B.V., Maastricht, the Netherlands) and FRIEND (Basilio et al., 2015) came out and enabled researchers to implement rt-fMRI neurofeedback easily. In the present day, rt-fMRI neurofeedback is used in different labs to answer different questions. Its applications for research and treatment will be discussed below.

1.1.2. Applications of rt-fMRI

All the developments mentioned above facilitated the online analyses of fMRI data and some offline methods became feasible online as well, e.g. pattern classification, which was used to decode mental state, was offline (for review see Haynes & Rees, 2006). Offline pattern classification enabled researchers to 'read brain' with a delay of hours. With the help of rt-fMRI, researchers can predict one's mind before the participant communicates with 70% accuracy (Hollman et al., 2011). The field keeps growing, now there are two available methodologies for rt-fMRI brain state classification: 1) pattern matching based on task-specific 2) machine learning based brain state classification (Wang & Wu, 2018).

Brain-computer interference (BCI) technique enables one to control external devices by brain activity and it is studied with EEG with patients such as paralysis patients (for review see Birbaumer & Cohen, 2007). As mentioned above, one of the advantages of rt-fMRI over rt-EEG is its easiness to learn. By utilizing rt-fMRI pattern classification healthy participants were able to navigate in a virtual maze (Yoo et al., 2004). It leads to expect that rt-fMRI BCI can be used with

patients to control some external devices or also to communicate in cases like lock-in syndrome, which causes paralysis with intact consciousness, and patients with vegetative state (DeCharms, 2008).

The most prominent use of rt-fMRI is neurofeedback. The rt-fMRI neurofeedback setup is comparable to regular fMRI experiments where the participants lies in the scanner and views some stimuli on the screen and performs a task during the scanning. The differences are that in the rt-fMRI neurofeedback experiment the data is analyzed as it is collected, the activity is converted into a feedback, which can be continuous or intermittent (Emmert et al., 2017a) and the task is to control the neural activity (please see Figure 1).

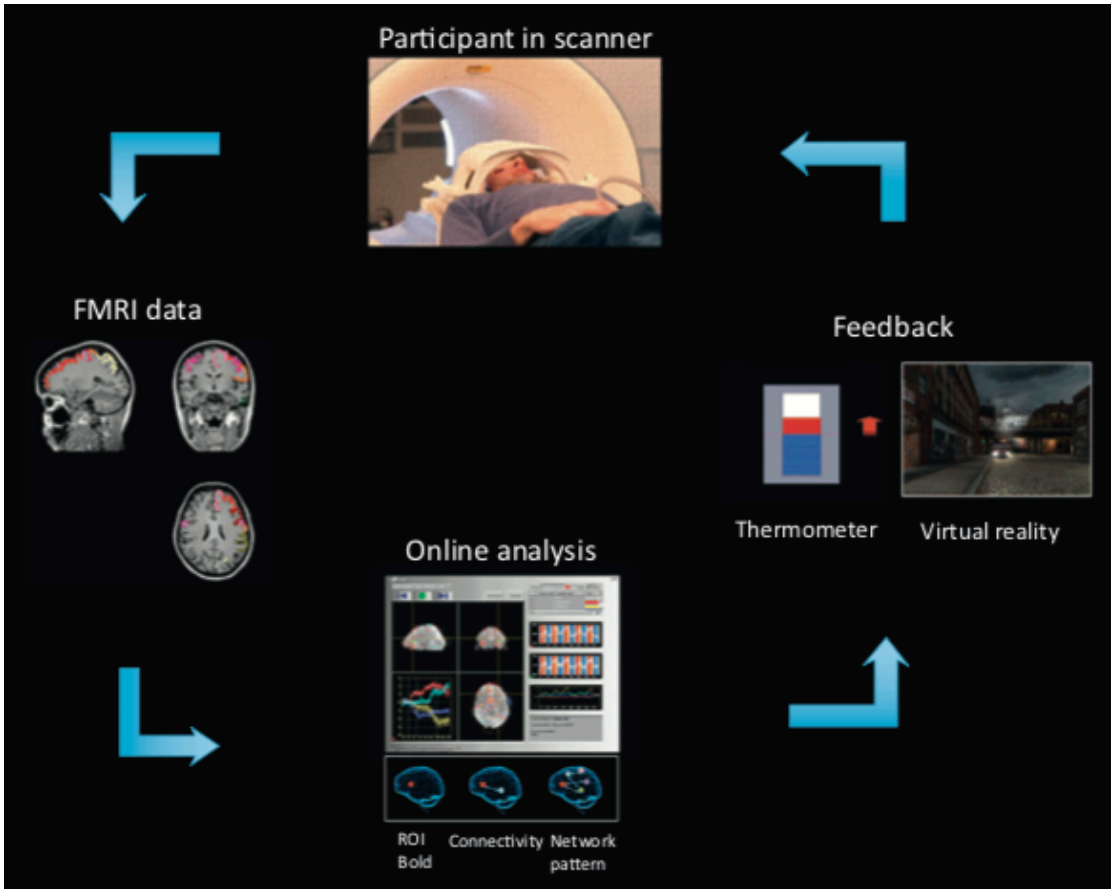

Figure 1. Overview of a rt-fMRI setup. The signal is acquired from MR, preprocessed, and analyzed. The result of analysis is presented back to the participant as feedback (adapted from Birbaumer et al., 2013).

In its short history rt-fMRI has been applied to many different brain regions such as anterior cingulate cortex (ACC – Weiskopf et al., 2004; Mathiak et al., 2010; Hamilton et al., 2011; Li etl al., 2013; Gröne et al., 2015; Dyck et al., 2016; Zilverstand et al., 2017), amygdala (Zotev et al., 2011; Paret et al., 2014; Gerin et al., 2016; Nicholson et al., 2017), auditory cortex (Yoo et al., 2006; Haller, Birbaumer, and Veit, 2010; Emmert et al., 2017a), basal ganglia (Sulzer et al., 2013 (substantia nigra); Greer et al., 2014 (nucleus accumbens), Kirsch et al., 2016 (striatum)), insula (Caria et al., 2007; Frank et al., 2012; Ruiz et al., 2013 Buyukturkoglu et al., 2015), motor areas (Christopher deCharms et al., 2004; Bray, Shimojo, & O'Doherty, 2007; Blefari et al., 2015), parahippocampal gyrus (Hohenfeld et al., 2017), posterior cingulate cortex (PCC – Zhang et al., 2012; Garrison et al., 2013), prefrontal cortex (Hampson et al., 2012; Scheinest et al., 2013; Sarkheil et al., 2015; Zhang et al., 2016; Algeria et al., 2017), visual areas (Shibata et al., 2011; Scharnowski et al., 2012; Amano et al., 2016). Scharnowski and colleagues (2015) demonstrated that it is possible to train subjects to control two distinct brain regions simultaneously, namely somatosensory cortex and parahippocampal cortex. There are also some studies investigating the possibility of feedback on connectivity of multiple brain regions. Zilverstand and colleagues (2014) found out that functional connectivity markers are unique and can be deployed in rt-fMRI set up. Spetter and colleagues (2017) demonstrated that the connectivity between two prefrontal regions – dorsolateral and ventromedial prefrontal cortices – could be increased. Another study compared the regular neurofeedback with neurofeedback enriched with functional connectivity and the group who received functional connectivity added

neurofeedback showed greater control over the region of interest, its connectivity with other brain regions, and greater modulation of behavior (Kim et al., 2015).

Subjects are able to learn to refine their neural activity without any explicit feedback or even without being aware of being trained (Shibata et al., 2011). But what does it mean? Is it a mere ability to control a brain region or does it transform into a cognitive or behavioral change? Many studies assessed cognitive and behavioral outcomes related to the region of interest as well in order to prove rt-fMRI neurofeedback's value. Some studies targeted the emotion network and measured the change in the emotion processing or mood (identification of feelings: Zotev et al., 2011; valence and arousal ratings: Caria et al., 2010; Greer et l., 2014; Gröne et al., 2015; Koush et al., 2017). Some studies aimed to show the enhancement in cognitive and motor tasks such as memory (Hohenfeld et al., 2017; working memory: Zhang et al., 2013; Sherwood et al., 2016; Zhang et al., 2016 ; autobiographical memory: Young et al., 2017), attention (Debettencourt et al., 2015), visual performance (color perception: Amano et al., 2016; visual extinction: Robineau et al., 2014; visual neglect: Robineau et al., 2019; visual detection: Scharnowski et al., 2012; reaction time: Bray et al., 2007), and motor performance (Blefari et al., 2015; Subramanian et al., 2011). Other studies aimed to improve physical and mental health. There is a line of rt-fMRI neurofeedback literature focused on craving and measuring the success of neurofeedback to decrease craving (cigarette craving: Canterberry et al.,2013; Hanlon et al., 2013; Li et al., 2013; Kim et al., 2015; Hartwell et al., 2016; alcohol craving: Karch et al., 2015; Kirsch et al., 2016 / hunger: Sokunbi et al., 2014; Ihssen et al., 2017; Spetter et al., 2017).

The ability to modify the neural activity attracted a great attention from the clinical researchers as neurofeedback can be used for therapeutic purposes. As DeCharms (2008)

highlighted in his early review that most of the pharmacological interventions are not targeting the brain regions specific enough and are having side effects. Considering that rt-fMRI neurofeedback has no reported side effects, it became an important field to explore whether it can be applied as a non-invasive methodology to target locally specific brain regions. The feasibility of rt-fMRI has been tested with different patient groups. A line of studies explored the impact of rt-fMRI neurofeedback on tinnitus (Emmert et al., 20017a; Haller et al., 2010). Another well-explored line is the probability to decrease the pain ratings with the hope to help chronic pain patients (Christopher deCharms et al., 2005; Emmert et al., 2014; Rance et al., 2014; Guan et al., 2015; Emmert et al., 2017b).

Relapses and treatment resistances are observed widely in pscyhiatric disorders, hence rt-fMRI neurofeedback is increasingly attracting attention in the clinical research. Major depressive disorder is one of the most widely investigated group (Linden et al., 2012; Young et al., 2014; Young et al., 2017; Hamilton et al., 2016; Zotev et al., 2016). In more complex disorders such as schizophrenia researcher might focus to different brain structure to improve different symptoms. Two studies targeted ACC, more specifically one study aimed to explore to get control over ACC in order to improve the impaired functions (Cordes et al., 2016) and the other study aimed to explore the effect of neurofeedback on audio-visual hallucinations (Dyck et al., 2016). Ruiz and colleagues (2013) provided schizophrenia patients neurofeedback on insula cortex to explore its effect on emotion recognition. A feasibility study revealed that patients with obsessive-compulsive disorder were able to reduce the activity in the anterior insula and this was also reflected in the positive behavior changes (Buyukturkoglu et al., 2015). Rt-fMRI neurofeedback has been tested for attention deficit hyperactivity disorder. Even though adult patients were able to increase their dorsal ACC activity, they did not differ significantly

from the control groups in terms of clinical outcome (Zilverstand et al., 2017), whereas adolescent patients who received right inferior prefrontal cortex neurofeedback showed a transfer effect when compared to the control group who received a neurofeedback from the left parahippocampal gyrus (Aelegria et al., 2017). Recently some new studies explored the application of rt-fMRI neurofeedback for post-traumatic stress disorder (PTSD) patients. As trauma related circuitry has been assigned to amygdala and ACC, studies aimed to get control over these regions (amygdala: Gerin et al., 2016; Nicholson et al 2017; Nicholson et al., 2018; ACC: Zweerings et al., 2018). PTSD will be discussed in the next chapters more in detail.

Additionally rt-fMRI neurofeedback has been investigated for the rehabilitation of neurological diseases such as neglect (Robineau et al., 2019), Parkinson's disease (Subramanian et al., 2011; Buyukturkoglu et al., 2013), and Alzheimer's disease (Hohenfeld et al., 2017). After the accumulation of the clinical literature on the rt-fMRI neurofeedback, Stoeckel and colleagues (2014) created a guideline for the optimization of the therapeutic use of rt-fMRI neurofeedback.

1.2. PTSD

Post-traumatic stress disorder (PTSD) might be caused by different traumatic triggers such as actual or threatened death, serious injury or sexual violation. The patient who develops PTSD might experience the trigger directly, witness it in person, finds out that it happened to someone really close, or is being exposed to the event's aversive details (American Psychiatric Association, 2013). Nevertheless the traumatic event should result in clinically significant distress or impairment in patient's everyday life in order to be diagnosed as PTSD. It is important to note that not everyone exposed to the same traumatic event develops PTSD.

Diagnostic interview data from National Comorbidity Survey Replication (Kessler et al., 2005) revealed that lifetime prevalence of PTSD in the U.S was 6.8%. Once someone develops PTSD, it has a severe impact on patient's quality of life in almost all fields (Warshaw et al., 1993). Warshaw and colleagues (1993) examined 688 subjects who entered the Anxiety Disorders research program and they grouped the subjects in 3 categories: no trauma, trauma without PTSD, and trauma with PTSD. In all emotional characteristics such as suicide attempts, hospitalization, alcohol or substance abuse the no trauma group was affected least and trauma with PTSD group most. Trauma with PTSD group needed the highest percentage of public assistance and they also showed highest percentage of unemployment across groups.

1.2.1. Symptoms

In the latest Diagnostic and Statistical Manual of Mental Disorders – DSM V – PTSD was not classified as an anxiety disorder anymore, but it received a new section called Trauma- and Stress-or-Related Disorders. There are multiple criteria for symptoms to diagnose PTSD. After experiencing a traumatic event as explained above, one should re-experience the event by nightmares, flashbacks, remembering the unwanted upsetting memories, or experiencing emotional distress or physical reactivity after exposure to traumatic reminders. Avoidance is another criterion and PTSD patient is expected to avoid trauma-related thought, feelings or any reminders.

Negative thoughts or feelings compromise a part of the symptoms of PTSD. Patients should display at least 2 symptoms of the following for diagnosis: amnesia regarding the trauma, overall negative thoughts, exaggerated blame, increased negative affect or decreased positive affect, feeling isolated, decreased interest in any kind of activity. Trauma is expected to

elicit arousal or reactivity such as irritability or aggression, risky or destructive behavior, hypervigilance, heightened startle reaction, difficulty in concentrating and sleeping. At least two symptoms from arousal and reactivity are required for the diagnosis.

When a trauma exposed person shows the symptoms above for more than a month, not as a result of medication or substance use, and when these symptoms causes distress or functional impairment in one's life, then this person can be diagnosed as PTSD.

Additionally there might be two extra specifications. If the patient meets the criterion above and experiencing depersonalization or derealization, it is recognized as dissociative PTSD. The other specification is delayed PTSD and it is diagnosed, when the full diagnostic criteria met at least 6 month later.

Mental health specialists use these symptoms for the diagnosis. The changes in the behavior and mental well-being are also reflected in the brain. Neurobiological markers will be discussed in the next session.

1.2.2. Neurobiological Markers

As summarized above PTSD has many symptoms and creates a great deficit in the patient's life. PTSD can be traced back to 2100BC when Epic of Gilgamesh narrated the tale of Gilgamesh who showed the symptoms of PTSD and than it kept appearing in the literature as traumatic events such as wars and natural disasters are as old as humankind (Crocq and Crocq, 2000). After the World War I it attracted more attention as a result of drastic increase of the cases. Thanks to the recent advances in the neurobiology we know more about its reflection in the brain.

1.2.2.1. Functional Activity

Symptom provocation studies using trauma related stimuli identified 2 key regions for PTSD. Subjects with PTSD had increased activity in amygdala (Pissiota et al., 2002; Hendler et al., 2003) and decreased activity in ventromedial prefrontal cortex (vmPFC) (Lanius et al., 2001; Lindauer et al., 2004) when contrasted with neutral stimuli in comparison with healthy subjects.

Non-trauma related emotional stimuli provoke similar neural activity in the brain of PTSD subjects. Shin and colleagues (2005) found out that patients showed exaggerated amygdala and diminished vmPFC activity as a response to fearful faces contrasted with happy faces in comparison to healthy controls. The paradigm required passively viewing of overtly presented faces. Alternatively another research group investigated the effect of nonconscious face stimuli processing (Bryant et al., 2008a). PTSD subjects showed increased amygdala and dorsal mPFC activity as a response to masked fearful faces contrasted with neutral faces. Lack of decreased activity in mPFC was interpreted as impairment in mPFC activity being limited to conscious fear processing.

In addition trauma-related emotional cognitive performance seems to be impaired in PTSD patients (Shin et al., 2001). Emotional Counting Stroop task requires participants to count the number of displayed words, which can be neutral or emotional. In this study emotional words were either general negative words or words chosen from a list of negative combat-related words to be shown to combat veterans with PTSD or without PTSD. PTSD group performed slower in response time in comparison with the control group across all conditions. Patients' impaired performance was not limited to behavior; they also did not show any increase in rACC activation, whereas combat veterans without PTSD showed increased activation in rACC for the combat vs general and combat vs neutral conditions. The attenuation

of rACC activity during a performance interference task was interpreted as rACC being mediator of distress and arousal upon exposure to trauma-related reminders.

Hippocampus is the third region, which has been associated with PTSD. A study with childhood abuse and PTSD, childhood abuse without PTSD, and healthy controls revealed hippocampal dysfunction during a verbal memory task in PTSD group (Bremner et al., 2003). The analysis showed an additional structural aspect that PTSD group had smaller hippocampal volume in comparison with two control groups. The functional difference was still significant even after correcting for hippocampal atrophy.

Above mentioned three key regions' abnormal activities differentiate a PTSD affected brain from a non-PTSD affected brain. Rauch and colleagues (2006) came up with a neurocircuitry model to explain what is happening in the PTSD affected brain and how these changes relate to the symptoms. They define PTSD as amygdala driven disorder. Hyperactivity of amygdala leads to hyperarousal, hypersensitivity to threat related stimuli, and enduring memory of the traumatic event. Hypoactivation of vmPFC including rACC, mPFC, subcallosal cortex (SG – subgenual ACC), and OFC results in a weak top-down control over amygdala, causes the inability to divert the attention from the trauma related stimuli, and culminates in no extinction of fear response. Hypoactivation of hippocampus contributes to uncontrolled hyperactivation of amygdala, impairs the ability to identify safe context and explicit memory overall. They also argued that when a fear conditioning happens with premorbid hyperactivity of amygdala, hyperactivity of vmPFC and hippocampus, excessive susceptibility to stress, it gives rise to PTSD. Additionally when PTSD becomes chronic, it might lead to magnification of the abnormal functioning in the brain.

1.2.2.2. Functional Connectivity

Typical functional MRI studies are task based and it gives insights on the neural aspects of the altered behavioral or cognitive performance in the clinical context. They might reveal changes in the neural activity in some regions, but they are unable to provide information on the connectivity of these regions. Resting state fMRI enables the researchers to measure the spontaneous modulations of the activities in the absence of task. This technique leads to inclusion of expanded patient population as sicker disease population might drop out of the studies due to the inability to follow the task and also it provides insight on fundamental abnormalities independent of tasks (see Fox & Greicius, 2010 for the review on clinical applications of resting state functional connectivity).

Bluhm and colleagues (2009) found PTSD group showed less PCC/precuneus activity correlated with the default network in comparison with healthy control group. Further analysis revealed that healthy group had greater connectivity to the areas such as amygdala, hippocampus, and mPFC than PTSD group, which are associated with PTSD. Additionally Lanius and colleagues (2009) showed that PCC connectivity with perigenual ACC and right amygdala is correlated with the current PTSD symptoms. They recruited acutely traumatized subjects and they followed up with the patients 12 weeks to observe the progress of the disease. As a result, they found that the correlation of the PCC with right amygdala was able to predict the future symptoms as well. Ultimately resting state connectivity can be useful as a screening tool after the trauma to discriminate the individuals who are more likely to develop PTSD.

There are multiple symptoms of PTSD and they are reflected in the different brain regions as functional activity studies pointed. This differentiation is reproduced in resting state activity as well (Tursich et al., 2015). The study of the relationship between the PTSD symptom severity

and resting state connectivity of salience, default mode, and central executive network disclosed that hyperarousal symptoms were negatively correlated with connectivity of posterior insula/superior temporal gyrus within the salience network and depersonalization symptoms were negatively correlated with connectivity of perigenual ACC/vmPFC within the default mode network. Resting state connectivity can be used to study the symptom severity as well as to differentiate the subtypes, namely dissociative PTSD with depersonalization symptom. Another group investigated the flashback and dissociative subtypes of the PTSD with PPI analysis using task-based connectivity (Lanius et al., 2005). Dissociated PTSD group showed higher conversations between activations in right ACC and left ventral PFC when compared with flashback PTSD. Both groups displayed between group differences based on the subtypes using different techniques to measure the functional connectivity.

As above mentioned neurocircuitry model suggested, the amygdala vmPFC connection attracted some attention. Rabinak and colleagues (2011) investigated the connection between amygdala and other PTSD related brain regions in PTSD and combat exposed control groups. They reported a stronger connectivity between amygdala and insula in PTSD group in comparison with combat exposed control group, but they failed to show any difference between groups for amygdala and prefrontal connectivity. Another group investigated amygdala connection further by looking into sub-regions of amygdala (Brown et al., 2014). They noted that PTSD group had a stronger basolateral amygdala complex connectivity with the perigenual ACC, dorsomedial PFC, and dorsal ACC than combat exposed control group and the control group had a stronger basolateral amygdala complex connectivity with the left interior frontal gyrus than PTSD group. Other sub-regions did not reveal any significant difference across groups. Kim and his group (2010) examined the amygdala and connectivity vmPFC with healthy

subjects by taking anxiety into consideration. Low anxious group showed positively correlated amygdala and vmPFC activity during resting state, whereas high anxious group showed negatively correlated activity.

There are also task-based connectivity studies. Stevens and colleagues (2013) presented fearful and neutral faces to PTSD patients and trauma exposed control group and they found PTSD group had a decreased amygdala and vmPFC connectivity in addition to the increased amygdala activity in response to fearful stimuli than control group. A symptom provocation PET study reported that there is an effective connectivity from amygdala to visual cortex, subcallosal gyrus, and ACC in PTSD group (Gilboa et al., 2004).

Functional connectivity studies were able detect some differences between PTSD and control groups, however they are inconclusive. There is a need for further examination in this field.

1.2.2.3. Structural Neuroimaging

Structural neuroimaging studies found three regions standing out in consistency with the functional activity studies. Hippocampus, amygdala, and ACC are the mostly studied regions. Karl and colleagues (2006) have systemically reviewed and analyzed existing literature on the structural changes in PTSD. They found decreased volume in hippocampus, amygdala, and ACC in PTSD group in comparison to healthy controls and traumatized controls. Smaller hippocampal volume has been observed in traumatized controls in comparison to healthy controls. Analysis of pediatric PTSD group did not show volumetric difference in hippocampus. This finding led authors to conclude that hippocampal difference can be noticed in the adulthood.

A recent meta-analysis study examined 59 volumetric analyses from 44 articles including 846 PTSD patients, 520 healthy controls, and 624 traumatized controls (O'Doherty et al., 2015). This meta-analysis revealed reductions in volume of the three regions. Subjects with PTSD had a decreased hippocampal volume, which was more exaggerated in the left hippocampus. Even though PTSD subjects had smaller amygdala in comparison to healthy subjects, they did not differ from the traumatized control group. Finally ACC was found to be smaller in PTSD group. These findings are in line with the observed deficiencies in salience network and default mode network. Slight differences between two meta-analysis studies might be due to the accumulating studies in the literature.

An interesting monozygotic twin study showed that smaller hippocampus is a risk factor for developing PTSD (Gilbertson et al., 2002). Researchers identified that the size of the hippocampi of both PTSD patient and patient's healthy twin correlated negatively with disorder severity. Even though smaller hippocampus is a risk factor to develop PTSD, developing PTSD leads to an additional hippocampal volume decrease. Another monozygotic twin study from the same group using the same dataset showed that PTSD causes volume loss in ACC (Kasai et al., 2008). Ultimately, the group concluded that hippocampal volume constitutes a risk factor, however the change in the ACC volume points to acquisition of PTSD.

1.2.2.4. Animal Studies

In animal models of PTSD, fear conditioning and extinction are used widely. Morgan and colleagues trained rats in a Pavlovian fear-conditioning paradigm pairing presentation of a tone as conditioned stimulus and foot shock as unconditioned stimulus (1993). Freezing behavior was the measure of the conditioned emotional response. Lesion in mPFC did not change the fear

conditioning, but rats with mPFC lesion did not show extinction when compared to sham lesion group and non-surgery group.

Milad and Quirk (2002) recorded rats' infralimbic activity, which is Brodmann area 25 (encompassed by ACC) in human, during fear conditioning and extinction. They found that there is variability in conditioned emotional response, some rats freeze less, which constitute high-recovery group and the others freeze more, which forms the low-recovery group. The response to the conditioned stimulus in infralimbic cortex reflected extinction memory and high recovery group showed higher activity in their infralimbic cortex. Subsequently Milad and Quirk stimulated the infralimbic cortex and observed facilitation in extinction learning. They argued that the stimulation of vmPFC in PTSD patients might enhance extinction learning.

1.2.3. Treatment & Prevention

The prevalence of trauma exposure is quite high. A nationwide survey in the US found that 60.7% of men and 51.2% of women of a 8098 respondents in were exposed to a traumatic event as least once in their life and the estimated lifetime prevalence of PTSD was calculated as 7.8% (Kessler et al., 1995). PTSD affects many people causing great impairment in their lives, that's why understanding which treatments work the best and also why some people do not develop PTSD after trauma exposure is crucial.

1.2.3.1. Treatment

Stein and colleagues (2006) reviewed 35 short-term randomized controlled trials of pharmacotherapy and they found that only in the half of the trials symptom severity was significantly decreased in the medication group in comparison with placebo. Selective serotonin reuptake inhibitors (SSRI) stand out from these successful trials.

Cognitive behavioral therapy (CBT) is the most widely tested and proved to be efficient psychotherapy treatment (Foa & Meadows, 1997). As neurocircuitry model by Rauch and colleagues (2006) suggests PTSD is characterized as a fear conditioning extinction deficit and CBT mostly focuses on exposure-based treatments. First study investigating CBT's impact on functional abnormalities reported that subjects with PTSD showed increased bilateral rACC and right hippocampus activities and no difference in amygdala activation after the treatment when contrasted with the before treatment scans (Felmingham et al., 2007). Additionally, recovery correlated positively with the change in the right rACC and negatively with the activation in the bilateral amygdala. Even though CBT is found to be the most efficient psychotherapy, a meta-analysis revealed that 67% of the patients who complete the therapy recover from PTSD and the recovery rate dropped to 56% when the drop outs were included (Bradley et al., 2008). Given the above it is crucial to be able to classify patients who can benefit from the treatment. Bryant and colleagues (2008b) scanned PTSD patients while viewing passively masked neutral and fearful faces prior to their CBT and they also followed up with a questionnaire to assess the treatment response after 6 months of completion of the therapy. The recovery rate was 50%, which was compatible to the meta-analysis. They reported that increase in bilateral amygdala and right ventral ACC was a predictor of non-responders and greater dorsal ACC activity was an indicator for responders. The authors concluded that having overactive fear processing network might lead to prevent the therapy success. Dickie and colleagues (2011) studied the impact of recovery after the psychotherapy, which was not specified by the authors. The comparison of pre- and post-psychotherapy revealed that amygdala and vmPFC activity were correlating with current symptoms, yet the functional changes in the hippocampus and subgeniual ACC were markers for recovery. Malejko and colleagues (2017) systemically reviewed the impact of

psychotherapeutic treatments. They noticed that PTSD recovery was associated with decreased activity in amygdala and insula, increased activity in dorsal ACC and hippocampus after the treatment. Elevated activity in dorsal ACC prior to treatment constituted a predictor for treatment success, whereas elevated amygdala and insula activity was associated with treatment failure. Even though the predictor regions for success and failure are correlating highly with the symptom severity, the authors fail to discuss this point.

Thomaes and colleagues (2014) reviewed the literature to detect change in the brain structure and function as a result of pharmacological and psychological treatment. Their review concluded that pharmacotherapy is helpful to recover from the structural abnormalities and psychotherapy is more successful to normalize the functional abnormalities. Their review included 3 structural studies measuring pharmacotherapy impact and 2 of them used SSRI treatment, which resulted in significant hippocampal volume increase, whereas the other study used phenytoin, which failed to contribute to hippocampal volume increase. There was only one structural brain change associated with psychotherapy (Lindauer et al., 2005) and it did not reveal any significant results. Thirteen functional studies investigating the impact of the psychotherapy indicated that psychotherapy might lead to decrease in amygdala activation and increase in PFC, dorsal ACC, and hippocampus activity. Two SSRI studies found increase in PFC activity after the treatment. As there are not many studies investigating the impact of treatments, there is a need for replication to confirm the results.

1.2.3.2. Prevention

Many people are exposed to at least one traumatic event throughout their life, but majority of them do not develop PTSD. Identifying the preventing factors might help many people who are suffering from PTSD.

Meta-analyses revealed some predictor factors such as prior trauma, family psychiatric history, perceived life threat during the trauma, social support, and peritraumatic psychological processes constitute the risk factors to develop PTSD (Brewin et al., 2000; Ozer et al., 2003). Some neural markers were identified to be preventive as well. A PET study found that recently traumatized subjects who did not develop PTSD except one subject showed functional interactions between amygdala, perirhinal cortex, and ACC/mPFC regions in comparison to healthy controls (Osuch et al., 2008). Researchers interpreted the decreased interaction of amygdala with other regions and increased ACC/mPFC activity as a sign of resiliency against PTSD.

1.3. Aims of the Thesis

The neural mechanisms underlying PTSD are well studied in the recent years. We have a general understanding of the functional changes happening in the traumatized brain with and without PTSD. Meta-analysis and review articles on functional activity of PTSD all pointed to the same regions: hyper activity in amygdala and hypoactivation in ACC and hippocampus (Bremner 2007; Etkin & Wager, 2007; Hughes & Shin, 2011; Robinson & Shergill, 2011). Even though the directionality of the abnormal activity stayed inconclusive in the patient studies, Etkin and colleagues were able to establish the ACC amygdala connectivity with PPI analysis and they disambiguate the direction being from ACC to amygdala by analyzing the data further with

effective connectivity in healthy subjects while subjects were resolving emotional conflict through top-down regulation (2006). After reviewing different human and animal models Hamner and colleagues (1999) also concluded that ACC is the gate to amygdala and its dysfunction enables amygdala to be hyperactive. For this reason addressing ACC for the therapeutic intervention would improve the overall disrupted network in PTSD.

Nevertheless ACC forms relatively large area in the brain and it encompasses distinct cytoarchitectural regions such as BA24, BA25, BA32, and BA33. Bush and colleagues (2000) developed a theory to explain ACC's heterogeneous functionality. After reviewing anatomy and lesion, imaging, EEG, developmental, and animal studies, they identified cognitive and emotional divisions; dorsal and ventral ACC respectively. Drevets and Raichle (1998) identified ventral ACC as part of emotional processing network and dorsal ACC as part of cognitive function network in fMRI research's early days and they pointed to the reciprocal suppression of these two networks. Even though ACC abnormality is frequently reported in PTSD studies, many failed to give specifications. Etkin and Wagner's (2007) meta-analysis of emotional processing in PTSD disclosed the differentiation in ACC during the emotional tasks. They reported that rACC and vmPFC are related to emotion regulation and dACC and dmPFC are linked to the emotional awareness. Both of the pairs were hypoactive, however the authors underlined the dissociation between the two systems. In the conclusion they advised the new treatments to target emotion regulation system. Furthermore researchers were able to facilitate the recovery in the animal model by stimulating the infralimbic cortex, which is the equivalent of Brodmann area 25 in human brain and they also pointed the importance of replicating these findings with human (Milad & Quirk, 2002).

The projects included in this thesis aimed to provide a tool to help PTSD patients to achieve to upregulate their rostral ACC encompassing BA25 in order to facilitate the extinction of the fear conditioning.

1.3.1. Project 1 – Validation of the methodology with healthy controls

The aim of the first project was to train healthy subjects to get control over their rostral ACC. ACC was the first brain region targeted with real-time fMRI neurofeedback by Weiskopf and colleagues (2003). Nevertheless they provided neurofeedback from both rostral-ventral ACC and dorsal ACC at the same time. Gröne and colleagues (2015) underlined the importance of choosing only one subregion of ACC either rostral or dorsal.

In the current study, the target region was located with functional localizer. Neutral, happy, and fearful Ekman faces are used as the localizer run (Ekman & Friesen, 1975). To inform the participants about the possible strategies and the target regions' function is optional in the literature and the participants were informed in this study as suggested by Linden and Turner to accelerate the training especially in patient studies (2016). An early meta-analysis of 55 fMRI and PET experiments on emotion revealed that recalling emotional memories leads to an increase in ACC and insula activity (Phan et al., 2002). Based on these findings the participants are instructed that the target region is related to emotion processing and they might use emotional memories to upregulate the region, nevertheless they are free to change the strategy and they can explore different strategies until they believe they find the best one for themselves. The localizer was repeated at the end in order to detect any neural changes, which might be due to the neurofeedback.

The study included male and female healthy control subjects in order to test the paradigm with healthy population first. We hypothesized that we might found some differences between male and female groups due to the differences in emotion processing (Whittle et al., 2011).

1.3.2. Project 2 – Application of rt-fMRI neurofeedback of ACC with PTSD patients

After the validation of the paradigm second project aimed to apply the rACC neurofeedback to PTSD subjects. The same methodology was used. This time male population was excluded as the first project revealed a serious gender difference for the paradigm. Additionally a review article of functional neuroimaging studies in PTSD highlighted the importance of focusing on a single sex in PTSD studies due to the great functional variability between male and female PTSD groups (Francati et al., 2007).

We hypothesized we would find less activity in the amygdala in PTSD groups as a result of successful rACC upregulation.

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2. Manuscripts of Unpublished Studies

2.1. Study1: Gender differences in the ability to regulate rACC with real-time fMRI neurofeedback

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2.1.1. ABSTRACT

Objectives: Most of the rt-fMRI studies in the real-time fMRI (rt-fMRI) literature included a small number of participants. We targeted rostral anterior cingulate cortex (rACC) which is a brain region involved in emotion regulation with thirty-two participants. Emotion regulation revealed differences in strategies and neural activity across sexes. We investigated the impact of sex difference in the rt-fMRI neurofeedback targeting a brain region associated with emotion regulation.

Methods: We recruited 32 participants (16 males and 16 females). We located their rACC with a functional localizer consisting of emotional face pictures from Ekman faces. Subjects learned to upregulate their rACC during four neurofeedback runs. We repeated the functional localizer run at the end to observe the impact of the neurofeedback on neural processing of emotional faces.

Results: Eight out of sixteen female participants gained control over their region of interest and four out of sixteen male participants learned to upregulate their rACC during four neurofeedback runs. We did not find any difference in neural activity for the localizer run across the sexes. However we found a difference between learners and non-learners that non-learners recruited more brain regions during neurofeedback runs.

Interpretation: The gender difference in learning to control brain activation is reported first time to our knowledge. This difference might be due to the emotion regulation, which was documented well in the literature, or it might be specific to rt-fMRI neurofeedback.

2.1.2. INTRODUCTION

The term biofeedback was first coined in 1969 and since then it has been used to describe the technique which provides the receiver‘s own physiological assessment to be regulated (Moss, 1998). The underlying mechanism is described as skill learning (Birbaumer, Ruiz, & Sitaram, 2013). Nowadays there are many different biofeedback techniques including heart rate variability (Siepmann et al., 2008), electromyographic biofeedback (EMG, regulating muscle action potentials) (Schleenbaker & Mainous 1993) and neurofeedback which means regulating brain activity based on feedback. Different methodologies can be used for neurofeedback as electroencephalography (Kotchubey et al., 2002), magnetoencephalography (Okazaki et al., 2015), near-infrared spectroscopy (Blume et al., 2017), and real-time functional magnetic resonance imaging (rt-fMRI) (Weiskopf et al., 2003). Since fMRI neurofeedback's first application by Weiskopf in 2003 the literature keeps growing. fMRI neurofeedback was utilized by applying different brain regions such as ACC (Weiskopf et al., 2003; deCharms et al., 2005; Zilverstand et al., 2017), visual areas (Amano et al., 2016), motor areas (Berman et al., 2012), and insula (Caria et al., 2007).

Any learning process is open to variability, since it is a subjective experience rather than an objective one. For example, Middaugh and colleagues displayed the differences in learning in two different biofeedback techniques in the Raynaud's treatment (Middaugh et al., 2001). Only 34.6% of the participants learned to control their physiological response to temperature biofeedback and 55.4% of the participants gained control over their response to EMG. Moreover, they pointed out that less male patients preferred biofeedback in comparison with female patients and they found that male patients were more likely to become non-learner than female patients. Only a few studies reported non-learners in fMRI neurofeedback literature. In

these studies ability to learn to control one's own brain activity varies between 46% and 77% for different brain regions (Bray et al., 2007 – 77% of the participants learned to control motor areas; Chiew et al., 2012 – 46% motor areas; Scharnowski et al., 2014 – 63% visual areas; Emmert et al., 2014 – 60.7% anterior insula or ACC; Robineau et al., 2014 – 57% visual cortex; Ramot et al., 2016 – 62.5% fusiform area or parahippocampal place area). None of these studies reported any sex difference for learners and non-learners. We expect to find a sex difference in the learning ability for a brain region related to emotion network, since its structural and functional differences across sexes are well documented (Sacher et al., 2013; Stevens & Hamann, 2012).

There is a growing literature showing the difference between male and female brain on different levels. Even though there are many inconclusive findings in the field, one of the most frequent findings is that men have bigger overall brain volume then women (Sacher et al., 2013). A meta-analysis revealed overall brain volume difference between males and females for all age ranges and females had larger volumes in anterior cingulate gyrus (Ruigrok et al., 2014). A voxel-based morphometric study measuring 411 subjects also found that female subjects had more grey matter volume in dorsal anterior, posterior and ventral cingulated cortices in comparison with male subjects (Chen et al., 20017). Additionally, resting state connectivity was found to be a good marker for sex difference in the brain. Zhang and colleagues were able to predict the sex with 87% accuracy by only analyzing the resting state connectivity (Zhang et al., 2018). Another study using anatomical and diffusion MRI found sex differences in the regions which are involved in cognitive networks such as social cognition, reward-based learning, decision making, and visual-spatial skills (Feis et al., 2013).

If we switch our focus to emotion, then the sex difference attracts even more attention. Solcova and Lacev investigated the emotions on behavioral and physiological level (Solcova & Lacev, 2017). Women scored higher than men in self-report of valence (both for positive and negative emotional stimuli) and intensity (only for negative emotional stimuli), however the physiological tests such as heart rate, skin conductance, and more did not reveal any significant difference for positive and negative emotional stimuli except in finger skin temperature. The authors concluded that women and men might experience emotions differently. However their body did not react differently on physiological level. Whittle and colleagues' review on sex differences in the neural correlates of emotion pinpointed the involvement of limbic system including amygdala, ACC, and thalamus during women's emotion perception in comparison with men and involvement of prefrontal and parietal regions for the opposite condition, which led the authors to conclude that both sexes rely on different strategies and brain regions during emotion perception (Whittle et al., 2011). Meta-analysis on emotional processing including 18 articles revealed many differences between sexes, in accordance with this study's interest rostral anterior cingulate cortex was found to be more activated in women in comparison with men (Sacher et al., 2013). Another meta-analysis including 44 studies showed that during processing of all emotions women had more ACC activation than men (Stevens & Hamann, 2012). On the contrary, another meta-analysis found out more mPFC, ACC, and thalamus activity in men than women and more amygdala, hippocampus, and midbrain activity in women than men during emotional perception (Filkowski et al., 2017) and authors interpreted their results to support existing research on men regulating their emotions more successful than women. Another study also supported the idea of differentiation in the recruitment of strategies for emotion regulation (Mak et al., 2009). When subjects were not given any

strategies to regulate negative emotions, females used more emotion-focused strategies which resulted in more activations in emotional processing regions and males used more cognitive coping strategies which resulted in more activation in cognitive processing regions.

In summary, there is an observable differentiation in male and female brain on structural and functional levels. However, as there are many studies limiting their subjects to only one sex without giving any explanation, and in case the study includes both sexes, authors do not report data by sexes (Eliot 2011). Stevens and Hamann (2012) concluded there is a need to consider sex as an important factor in emotion research as a result of their meta-analysis on emotion processing. Rt-fMRI neurofeedback studies either lacked to include both sexes or to report any results concerning sex differences.

In the current study, we recruited female and male healthy subjects to train their rACC as part of the emotion network. Based on the existing findings, we expected to find a sex difference in the recruited brain regions to achieve the goal.

2 .1.3. METHODS

2.1.3.1 .Participants

Nineteen female and seventeen male thirty-eight healthy volunteers participated in our study. Two female and a male subject had to be excluded, as no target area could be determined in the localizer run (“non responder”). Another female was discarded due to an incomplete dataset. The remaining subjects, sixteen female volunteers ranging in age from 21 to 33 (mean age = 25,56) and sixteen male volunteers ranging in age from 19 to 29 (mean age = 24) with no history of neurological or psychiatric illness, head trauma, or psychoactive substance abuse and no MRI contraindications were included in our analyses. They were

recruited from Ludwig-Maximilian University graduate students and paid 25€ each for participation.

The study protocol was approved by the ethics committee of Ludwig Maximilans University and written informed consent was obtained from all subjects.

2.1.3.2. Stimulus

2.1.3.2.1. Functional localizer

For the determination of the Region of Interest (ROI) in the subgenual ACC as target area for neurofeedback, a functional localizer with emotional stimuli was performed using a block design paradigm.

Stimuli consisted of 16 black and white pictures of the faces of 8 individuals (4 men, 4 women) expressing happy and fearful emotions from Ekman and Friesen (1975). They were grouped by expression type and gender into 4 sequences (Figure 1a and 1b), each lasting 40 s (each picture was displayed two times in a block for 3 s in a randomized order and was followed by blank screen for 2 s). Two sequences of the same expression type of both genders were summed up to a stimulus block (happy/fearful faces blocks); each block was shown twice.

In order to have a high contrast in comparison with emotional facial expression, low-level fixation (black star on a grey background, Figure 1c) was presented as baseline. In the resulting paradigm (6min 40s), five baseline blocks (40s) alternated with four stimulus blocks (80s) (Figure 2).

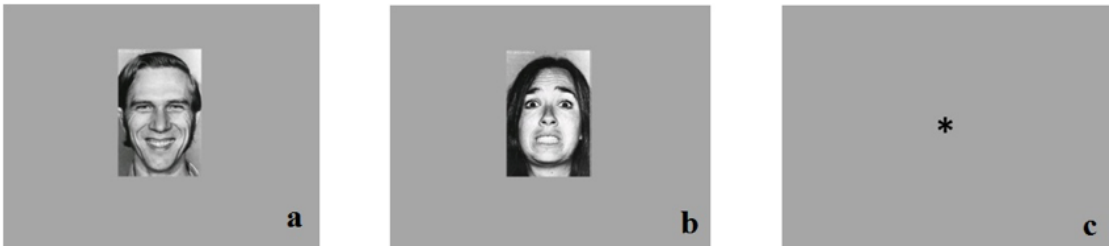

Figure 1. Stimuli in localizer. **1a** a male face of happy expression, **1b** a female face of fearful expression, **1c** low-level fixation screen (Adapted from Demircapa, 2012).

The instruction that was presented to the subjects in the scanner immediately before the localizer run started was 'Please attend and pay attention to facial stimuli and the related emotion. During the star, please stay fixated and try to minimize your thoughts'.

After image acquisition, a radiologist and a neuro-cognitive psychologist agreed on the target area in the ACC for creating the functional ROI using the map of the online-analysis. The brain area with the highest effect for emotion (happy and fearful faces pooled together) versus low-level fixation in the subgenual ACC, which has been measured by the beta values, was set as ROI. In case of no activation in the subgenual ACC, the ROI was set in the border area of the dorsal ACC. No strict regulation of size and shape was imposed.

Besides, after neurofeedback, a control run was performed corresponding to the localizer run in order to look for functional differences between both runs that might reveal training effects.

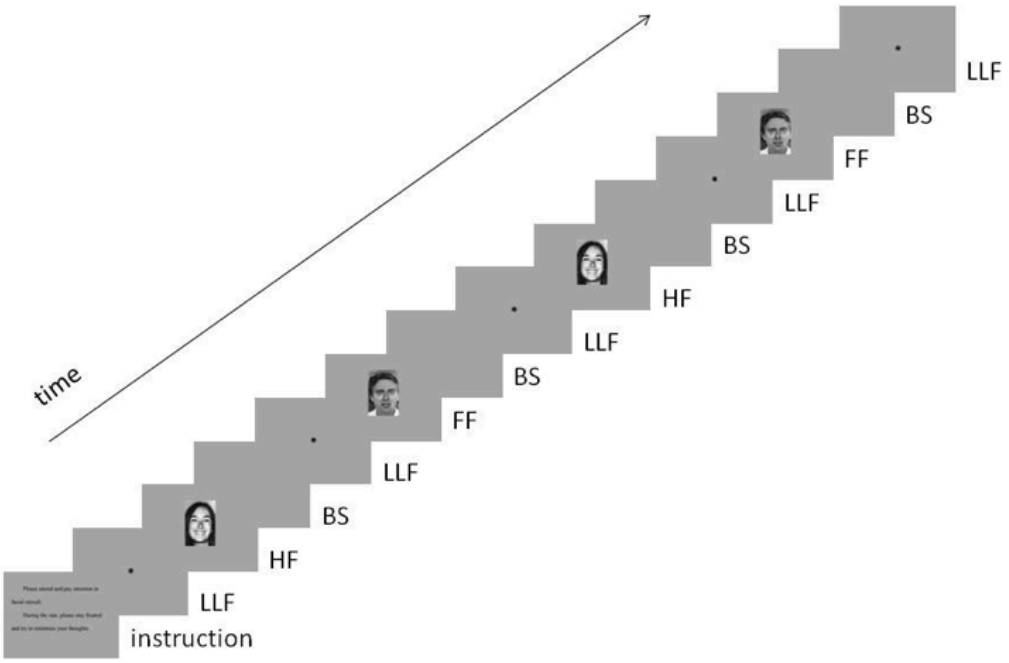

Figure 2. Experimental design. LLF = low-level fixation, HF = happy face, BS = blank screen, FF = fearful face. Localizer run starts with instruction for 10 seconds. Low-level fixation is followed by female and male happy faces. Second low-level fixation is followed by fearful faces. This sequence has been repeated one more time. Finally, localization run ends with a low-level fixation block (Adapted from Demircapa, 2012).

2.1.3.2.2. Neurofeedback

Subjects should learn to regulate their neural response in the target area of the ACC during four subsequently performed neurofeedback runs. Continuous visual feedback was presented to the subjects by a bar with ten squares (figure 3). Additionally, the subjects were verbally informed about their performance during the brakes between the neurofeedback runs. A single neurofeedback run consisted of 5 downregulation and 4 upregulation blocks. Each block

lasted 40 seconds At the beginning of the each block, the name of the block appeared and at the same time, the subjects were informed verbally via their headphones.

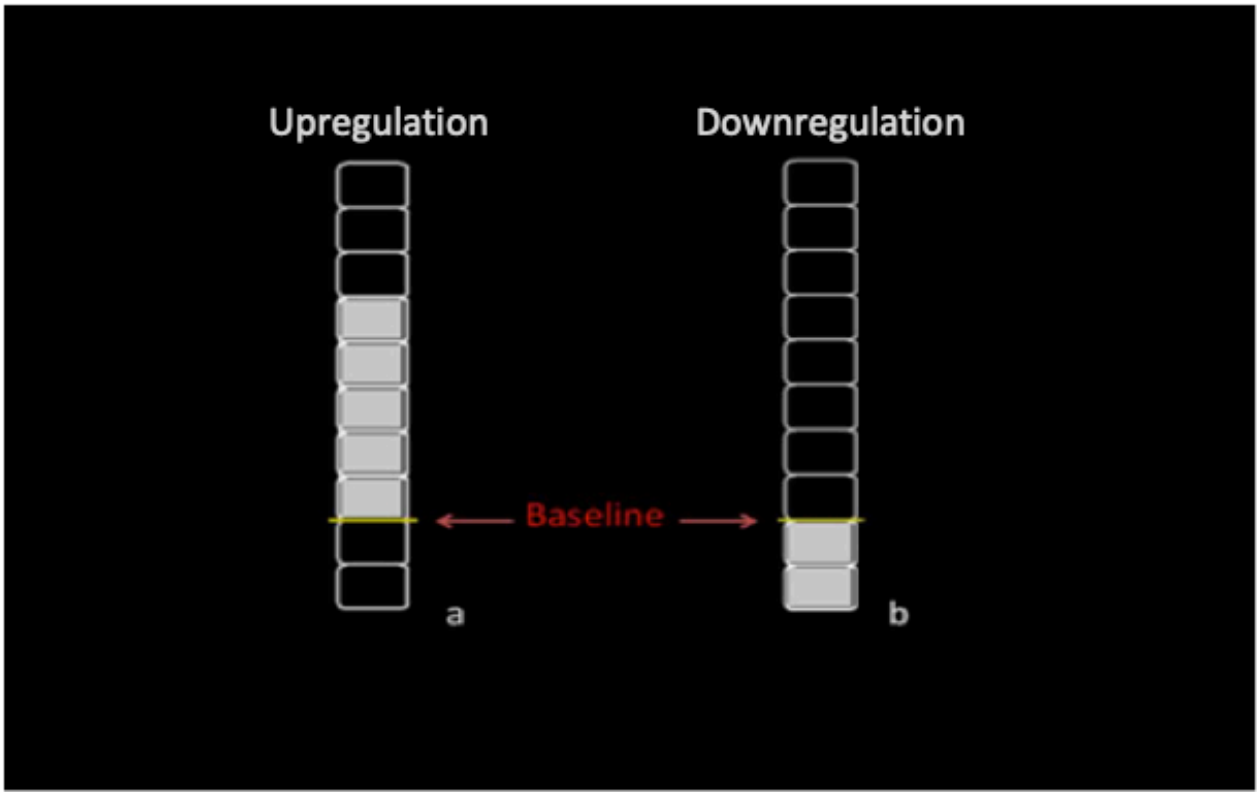

Figure 3. Feedback exemplars. **3a** the bar when subject succeeds an activation of ACC over the baseline. **3b** the bar when subject has an activation of ACC under the baseline (Adapted from Demircapa, 2012).

Subjects were instructed to upregulate their ACC activation during the upregulation blocks and to reduce their ACC activity during the downregulation blocks. Participants were proposed to think about their emotional memories to upregulate their ACC and to be meditative for downregulation blocks. Nevertheless they were instructed to change strategies as a trial and error method and not to stick with a strategy, especially if it is not working. They were set free in terms of trying out new strategies. Emphasis was put to the fact that target area was chosen due to emotional stimuli and the new strategies should contain an emotional aspect. As long as

subject found a method to control ACC activation, they are suggested to hold on to that strategy. Subjects were also informed about the nature of the BOLD signal and the latency in feedback up to 4-6 seconds due to BOLD signal in order to take it into account.

First run of feedback was thought as a familiarization phase with focus on the exploration of different strategies. With the second run they were expected to have a little bit experience and understanding of the method. In the third and fourth runs, they were asked to use the strategies, which they think, worked best.

2.1.3.3. Study design

Once the participant arrived, they were informed about the study, neurofeedback, and ACC. They were instructed to fill in questionnaires about demographics, health scanning questionnaire, verbal-linguistic intelligence test (WST, Aschenbrenner, Tucha, & Lange, 2000), and State-Trait Anxiety Inventory - A-State scales (STAI form 1, Laux et al., 1981). Following they participated in fMRI scanning in the following sequence order: (1) localizer run (determination of the functional ROI), (2) 1st resting state sequence, (3) four neurofeedback runs, (4) localizer control run (5) 2nd resting state sequence. Lastly, the anatomical scan was acquired. Finally, the participants received a questionnaire about rating the pictures of Ekman faces, Emotion Regulation Questionnaire (ERQ, Abler & Kessler, 2009), scales of emotional experience (Skalen zum Erleben von Emotionen - SEE, Behr & Becker, 2004), State-Trait Anxiety Inventory - A-Trait scales (STAI form 2, Laux et al., 1981), and Beck Depression Inventory (BDI, Hautzinger et al., 1994) to fill in them at home and post them back in two weeks.

2.1.3.4. Image acquisition

Subjects were scanned in a standard clinical 3 T whole body system (Phillips ACHIEVA/INGENIA 3T), equipped with a 32-element phased-array head coil. Functional data were acquired using BOLD sensitive echo-planar imaging (EPI) with a T2*-weighted gradient-echo sequence in axial orientation. Functional images of the localizer runs and neurofeedback runs were obtained with the following parameters: field of view (FoV): 230 x 230 x 104 mm; voxel size: 3.0 x 3.0 x 4.0 mm^3; imaging matrix: 76 x 77; time of repetition (TR): 2000 ms; time of echo (TE): 35 ms; flip angle (FA): 90°; number of slices: 25; number of volumes: 265 (localizer runs); 185 (feedback runs); SENSE: 1,8 (p reduction, AP). Sequences covered the whole cerebrum. Slices were positioned parallel to the connection line between anterior commissure and posterior commissure.

A high-resolution T1-weighted three-dimensional sequence was acquired for anatomical reference. Slices were positioned in sagittal orientation using the following imaging parameters: FoV: 240 x 188 x 220 mm; voxel size: 1.0 x 1.0 x 1.0 mm^3; TR: 8.2 ms; TE: 3.7 ms; FA: 8°; number of slices: 220; SENSE: 2,5 (p reduction, AP)/ 2 (s reduction, RL).

2.1.3.5. Data Analysis

The performance of the participants varied in neurofeedback runs. Two obligate conditions were used to classify them according their performance as learners: 1) Mean of beta value difference between up & down in 4 runs should be positive by exceeding 0.1, and 2) the participant's single beta values should be more than 0.25 each or should be increase with each sequent run– one exception was tolerated with respect to tiredness or attention distraction effects. If not, the participant is classified as non-learner. The further analysis was done to

compare female and male groups, but also to find common activation for learners and non-learner (see Figure 4a and 4b).

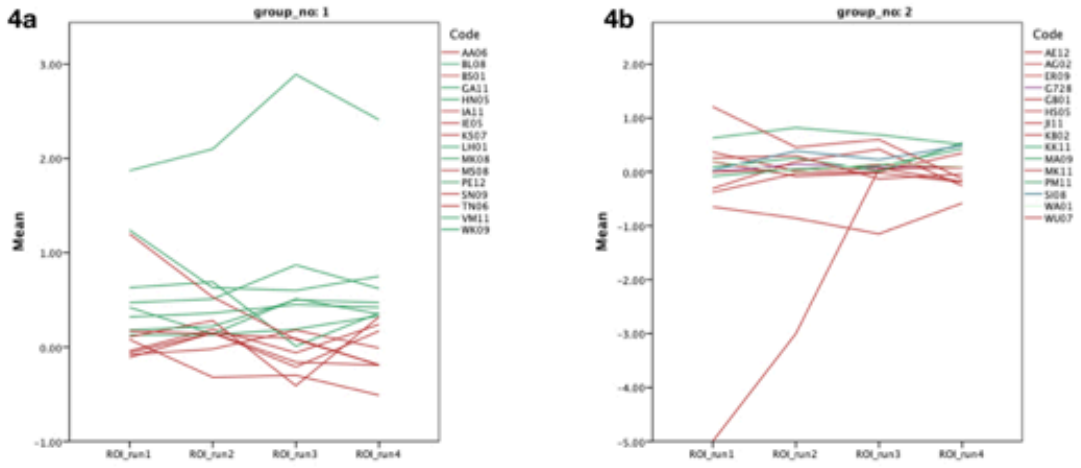

Figure 4. ROI activations, greens are learners and reds are non-learners **4a** beta values of ROIs of female participants during neurofeedback runs. There were 8 learners and 8 non-learners **4b** beta values of ROIs of male participants during neurofeedback runs. There were 4 learners and 12 non-learners.

The online analysis was performed with Turbo Brain Voyager software package Version 3.0 (Brain Innovation B.V., Maastricht, the Netherlands). For the localizer run, the online GLM was computed using two predictors emotional faces and low-level fixation, convolved with a hemodynamic reference function. The threshold was 2.0, which is corresponding to uncorrected 0.05 significance level. For the neurofeedback runs, the online GLM was computed using one predictor for the regulation state either up or downregulation, convolved with a

haemodynamic reference function. Only the highest activity in 33% of the voxels in the selected ROIs across three functional imaging slices were responsible for the neurofeedback signal.

The offline analysis was performed with the Statistical Parametric Mapping Software (SPM8, Welcome Department of Cognitive Neurology, London, UK). The first five volumes of each run were discarded due to T1 saturation effects. The remaining functional images were superimposed on 3D anatomical images. The complete data set was transformed into Talairach space through trilinear interpolation. Pre-processing of functional images was consisted of 3D motion correction, slice scan time correction, high pass temporal filtering (2 sines/cosines), and Boxcar predictors were convolved with canonical haemodynamic response function.

For the localizer runs, we ran 1 sample t-test by merging PTSD and control group together, conjunction analysis, contrasted PTSD and control groups, and also created learner and non-learner groups merging PTSD and control groups together. We compared happy, fearful, and resting blocks between pre- and post-neurofeedback localizers. For the neurofeedback runs we repeated the same tests and we compared upregulation and downregulation blocks. As two groups were significantly different from each other in age, age was added as regression in the group comparison.

Moreover, AAC mask from MarsBaR toolbox for SPM (Brett et al., 2002) and BA24s, BA25, BA32s, and BA33 masks (according to Palomero-Gallagher and colleagues' mapping of subgenual cortical areas (2015)) from Anatomy Toolbox for SPM (Eickhoff et al., 2005) were used for region of interest analysis. Then, activations were determined according to the clusters, which were automatically defined (minimum 20 voxels) by the software. Within each cluster of statistical significance, the peak t-test value were determined and its location was expressed in x, y, and z coordinates.

The questionnaires are analyzed with Statistical Package for the Social Sciences (IBM, SPSS version 20.0). For bivariate relationships we used two-tailed Pearson's r. Independent two-tailed t-tests were used to compare group differences in questionnaires. Two-tailed paired sample t-tests were conducted to measure the effect of neurofeedback on selected ROIs from localizer runs.

2.1.4. RESULTS

2.1.4.1. FMRI results

2.1.4.1.1. Localizer

Pre- and post-neurofeedback localizers were compared in order to measure the impact of neurofeedback on processing of emotional stimuli. No significant activation was found, when the data was FWE corrected.

2.1.4.1.2. Neurofeedback

Female and male groups were merged together in order to reveal the general effect of neurofeedback. Up- and downregulation blocks across four runs were contrasted (see Table4 and Figure8).

Table1: all participants Neurofeedback peak voxel coordinates table (FWE 0.05; cluster size > 20 voxels)

Analysis	Location	Clusters size	x y z	z-statistics
up-down all	r dorsal PCC	668	20.78 -36.0 26.44	5.87
	r ventral ACC		9.84 0.92 24.35	5.77
	r V1 & V2	230	6.97 -87.46 5.12	5.12
	l hippocampus	116	-31.55 -32.59 -6.55	5.89
	l caudate tail		-26.33 -40.56 17.11	5.09
	l PCC		-28.98 -47.88 5.56	5.08
	l PCC	102	-15.14 -51.01 8.2	5.85
	r retrosplenial CC	26	15.4 -48.37 8.96	5.60
down -up all	r visual association	634	31.62 -70.9 36.83	6.35
	r Wernicke's area		42.79 -56.72 35.66	6.13
	l Wenicke's area	355	-37.7 -50.71 34.87	5.98
	r visuomotor coord.	102	12.08 -71.58 44.54	5.95
	r PCC	44	3.93 -42.8 39.03	4.95
	r Premotor cortex	22	23.37 14.74 55.62	5.00
	r FEF		1.17 -34.41 39.77	4.90

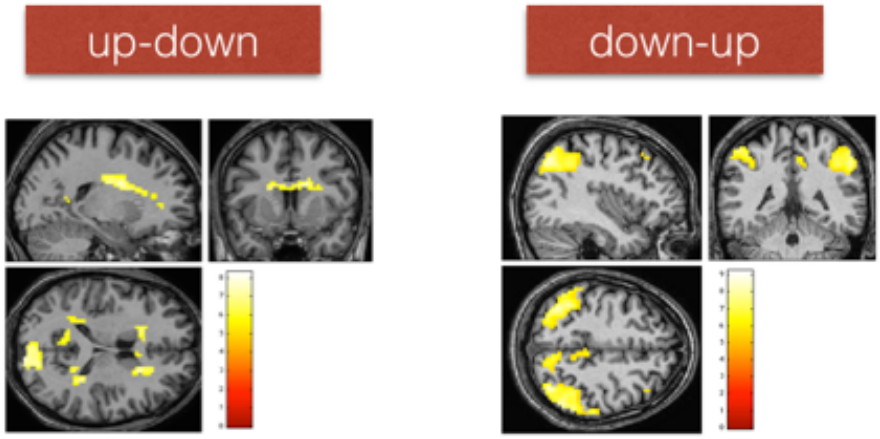

Figure5: All participants upregulation vs downregulation (FWE p<0.05).

Learners and non-learners from both female and male groups are merged together in order to observe non-gendered learner and non-learner commonalities. FWE corrected data did not reveal any significant results. The uncorrected results with significance p<0.001 are shown below (see Table 2 and Figure6).

Table2: Female + Male Learner vs Non-Learner Neurofeedback peak voxel coordinates table (p<0.001; cluster size > 20 voxels)

female+male non>learner				
upregulation all	r visuomotor ass.	29	17.73 -46.19 44.34	3.73
	r visuomotor ass		12.25 -45.64 38.9	3.67
downregulation all	r dACC	22	1.34 16.16 41.87	4.08
	l Fusiform Face	22	-45.72 -64.82 6.37	3.60

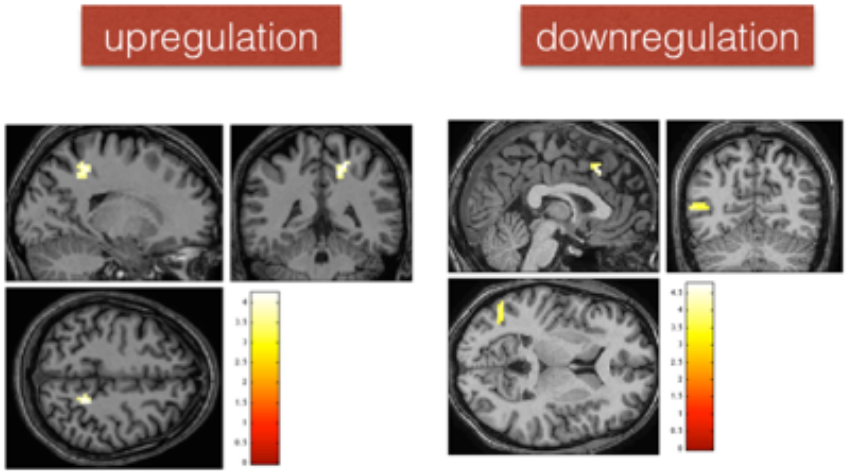

Figure6: Non-Learners > Learners (p<0.001).

2.1.4.2. Post-scanning Interview

In the post-scanning interview, participants reported how well, they thought, they could regulate their ACC and also how they felt at the end of experiment in a scale from 1 (bad) to 5 (well). The mean for their impression how well they regulate their ACC was 3.5 (SD = .87). There was no group difference between male and female participants (t=.808, p>.05). The mean for their feelings was 3.87 (SD =.87). No group difference was found (t=-1.228, p>.05). Female learner group (M=4.12, SD=.64) anticipated their performance better than female non learner group (M=3.87, SD=.99); t(14)=2.02; p<.05). This comparison was not made for male subgroups due to the unequal numbers of male subgroups. We pooled male and female participants together to create learner and non-learner groups. Anticipated performance comparison pointed to a strong trend in favor of learners (M=3.39, SD=.68) in comparison with non-learners

(M=3.23, SD=.91) (t=1.97, p=.057). Subjects reported their strategies for upregulation and downregulation blocks. Subjects used mostly anticipation of happy memories, imagination of beloved ones, and/or performing their hobbies for the upregulation blocks and concentration on fMRI noise, on screen, and/or meditation for the downregulation blocks.

2.1.4.3 Relation of ACC Activation with Questionnaires

ACC activations (BA 24s, 25, 32s, and 33) measured by MarsBar and Anatomy Toolbox were correlated with questionnaires individually for both groups with the aim to predict whether the participant can benefit from the neurofeedback based on their questionnaires results.

Female groups' STAI1 results correlated with up-down contrast of ACC activity (BA32s r=.583, p<.05). Independent t-test for questionnaires revealed a significant difference between male and female groups only for FDS test (t=-3.309, p<.01). However ROI correlations with questionnaires showed different results for male group. Suppression results for ERQ had a negative correlation with up-down activity for male group (BA24s r=-.610, p<.05; BA25 r=-.569, p<.05; BA33 r=-.499, p<.05). SEE overwhelming related questions correlated positively for up-down regulation contrast (BA25 r=-.629, p<.01; BA33 r=-.626, p<.01).

2.1.5 DISCUSSION

In the current study, we localized rACC functionally and fed back the activation to the healthy subjects. The success rate to modulate rACC was 37,5% (12 out of 32 participants were learner). Nevertheless there was an obvious sex effect. 50% of female participant showed a learning effect, whereas only 25% of male participants met the criteria for learning group.

When all participants were pooled together, we found a clear pattern for upregulation and downregulation. During the upregulation blocks participants had more activation in their ACC, PCC, retrosplenial CC, hippocampus, caudate, and visual cortex. These regions are all linked to autobiographical memory, remembering past, and imagining future (Bauer et al., 2016; Gimore et al., 2018). It is worth to mention cingulate cortex's role in performance monitoring (Holroyd et al., 2004; Gablentz et al., 2015). A meta-analysis on rt-fMRI neurofeedback revealed a network for brain regulation including anterior insula, basal ganglia, striatum ACC, dlPFC, vlPFC, temporaparietal area, visual association areas activations and PCC, precuneus, bilateral transverse temporal area deactivations (Emmert et al., 2016). However it is important to be aware of the fact that ACC is cytoarchitectually and functionally heterogenous (Vogt , 1993; Bush et al., 2000) and feedback related activation was found in dACC. Independent of this area, participants were instructed to regulate their rACC. During the downregulation blocks, participants had more activation in their visual association area, visuomotor area, Wernicke's area, PCC, premotor cortex, and FEF. We only replicated PCC activation from the meta-analysis results (Emmert et al., 2016). Most of the participants used meditation technique during the downregulation blocks and premotor area is known to play a role in the meditation (Fox et al., 2016).

Even though we found a sex difference in the ability to learn to modulate brain activation, we did not find any sex differences in the comparison of neurofeedback blocks. Neuroimaging studies showed that there is a functional difference during emotional perception (Stevens &Hamann 2012; Sacher et al., 2013) and also strategies differ according to the sex (Mak et al., 2009). We did not expect to find different strategies, because the participants were informed about the target area's function in order to increase the success rate as suggested by Linden

and Turner (2016). Nevertheless we found a difference between learner and non-learner groups. Namely non-learners recruited more brain regions during upregulation and downregulation blocks. Learner group anticipated their performance better than non-learner group. Non-learner group struggled to find a working strategy and had more unconfined activation. As Jeon and Friederici showed (2017) expertise leads to neural efficiency, this might explain the absence of activation in the learner group (learner>non). Additional dACC activation of non-learner group during the downregulation blocks might point to the error detection as non-learners were aware of their performance (Holroyd et al, 2004).

We have examined the correlation between the ACC activity during neurofeedback and the questionnaires. We found that men who had higher scores in suppression questions of emotion regulation questionnaire were less likely to achieve a positive activation difference in ACC between upregulation and downregulation blocks. John and Gross (2004) concluded that suppression is a less adaptive emotion regulation in comparison with reappraisal and individuals who used suppression experiences less positive emotions. Men use suppression as an emotion regulation method more than women (Abler & Kessler, 2009), though we failed to replicate this difference with our smaller sample size. We found a similar effect of STAI test for female participants. Women who scored higher in STAI-I (form A) test achieved a better difference between upregulation and downregulation blocks. STAI-I measures the current state of anxiety. Being more anxious prior to scanning could help women to be more focused and to achieve a better a difference between upregulation and downregulation blocks.

We repeated our functional localizer after the neurofeedback session in order to measure whether emotional faces are processed differently after neurofeedback session. However we failed to find any significant results. An fMRI study showed that adaptation to face stimuli led to

decrease in neural activity (Winston et al., 2004). Pre-neurofeedback localizer did not result in more activation in comparison to post-neurofeedback. It might be either due to neurofeedback effect or to small sample size. In order to rule out this possibility, the study needs to be replicated with a bigger sample size.

Overall, we did not find a sex difference in the functional aspect of the neurofeedback, however we observed a strong impact of sex on learning ability to regulate the brain activation. Our findings differ from existing results in the rt-fMRI neurofeedback. It can be related to the fact that zero results and "bad results" go unpublished many times and we do not have a statistic about it, because non-clinical fMRI studies are not pre-registered mostly (Thibault et al., 2018). fMRI sessions are still very costly and with this learning rate it might not be feasible to apply rt-fMRI neurofeedback as it is hoped. However defining predictive factors in experimental groups and applying them to bigger groups might be a solution. For our specific experimental setup we found that higher suppression scores for men and low STAI1 scores for women might be exclusion factors for rACC neurofeedback training. The present study attracts attention to diversity in the learning ability in rt-fMRI neurofeedback and the importance of definition of success criteria.

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2.2. Study2: Real-Time fMRI neurofeedback of ACC with PTSD patients

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2.2.1. ABSTRACT

Objectives: Post-Traumatic Stress Disorder (PTSD) treatments have low response rates and there is a need for a new treatment for non-responders. Real-time functional magnetic imaging (rt-fMRI) neurofeedback might be the next tool to treat the non-learner PTSD patients. We implemented rt-fMRI neurofeedback of rostral anterior cingulate cortex (rACC) with PTSD patients. We expected to find a change in the neural network as a result of neurofeedback.

Methods: 16 female PTSD patients and 16 female healthy controls participated in the study. All subjects attended a functional localizer run consisted of 8 happy and 8 fearful face pictures before and after 4 runs of neurofeedback of rACC neurofeedback.

Results: There was no difference between PTSD and control groups in pre- and post-localizer runs, however we found that PTSD group recruited more brain regions related to sensory processing in comparison to control group during the neurofeedback runs ($p<0.001$, uncorrected). PPI analysis did not reveal any difference between rACC and amygdala connection for any group.

Interpretation: Half of the participants were able to control their rACC independent of their group. There is a need for further investigation to find out the predictor factor for the successful control over rACC and whether the successful regulation would lead to any structural or functional changes in the brain.

2.2.2 INTRODUCTION

Post-traumatic stress disorder (PTSD) might be triggered by experiencing directly, witnessing, experiencing first-hand report of a traumatic event, or learning that a traumatic event affected a close person (American Psychiatric Association, 2013). DSM V first time classified PTSD under Trauma- and Stress-or-Related Disorders section thanks to increasing number of research in the field. PTSD is known to have a severe impact on quality of life of the patients and has long-lasting effects (Warshaw et al., 1993). Despite our growing knowledge on its mechanisms, only half of the patients are responding to psychotherapy (Bradley et al., 2005; Bryant et al., 2008) and only 59% of patients are responding to pharmacotherapy (Stein et al., 2006).

Neurocircuitry models of PTSD pointed to hyperactive amygdala due to hypoactivation of ventral medial prefrontal cortex (vmPFC) including rostral anterior cingulate cortex (rACC), which cannot express its top-down control on amygdala and hypoactive hippocampus, which is argued to be related to declarative memory impairments (Rauch et al., 1998; Hughes & Shin, 2011). Among these dysfunctional brain regions, Hamner and colleagues (1999) concluded that ACC is the gatekeeper for exogenous stimuli and its dysfunction leads to failure in the top-down control of amygdala-driven fear conditioning. In addition to the functional abnormality in the ACC, a structural MRI study showed decrease in grey matter of ACC (Kasai et al., 2008). Robinson and Shergill (2011) pointed out that structural and functional abnormalities lead to susceptibility to PTSD and developing PTSD exaggerates these abnormalities. Supporting these findings, high ACC activity was found to be protective against development of PTSD in motor vehicle collusion survivors (Osuch et al., 2008). Additionally, PTSD patients following cognitive-behavior therapy had more rACC and less amygdala activation as a response to fearful face

stimuli in comparison with pre-therapy (Felmingham et al., 2007). On the contrary, Bryant and colleagues (2008) found that higher activity of vACC was a predictor of non-responsiveness to therapy unexpectedly and they attributed this result to the nature of the rapid presentations of stimuli, which resulted in the engagement of bottom-up system rather than top-down. Animal models of PTSD also supports the importance of ACC. Milad and Quirk (2002) showed that rats which did not form extinction memory in response to fear conditioning were able to inhibit fear response when stimulated in the infralimbic cortex (it is equivalent of BA25, rACC in human). Stimulation of brain helped rats to overcome the exaggerated fear response. Even though same methodology is not applicable to human, neurofeedback might help PTSD patients to regulate their ACC, especially when patients are not able to benefit from psycho- or pharmacotherapy.

Neurofeedback is the learning mechanism where participants fed back or rewarded based on their ability to regulate a particular neural signal (Birbaumer, Ruiz, & Sİtaram, 2013). Electroencephalogram (EEG) neurofeedback is the method that participant learns to modulate own cortical oscillation by receiving information on the brain activity (Kamiya et al., 1969). Since its first use, it has been a promising tool to proximate abnormal activity of psychiatric disorders to normal. It has been applied with attention deficit – hyperactivity disorder patients (Mayer et al., 2016), major depressive disorder patients (Cheon et al., 2016), children with autism spectrum disorder (Wang et al., 2016), and also PTSD patients (van der Kolk et al., 2015; Nicholson et al., 2016).

EEG neurofeedback seems to be effective with PTSD patients. Research indicated that PTSD patients showed improvement in PTSD symptoms and affect regulation (van der Kolk et al., 2015; Gapen et al., 2016; for review see Reiter et al., 2016). One shortfall of the EEG neurofeedback despite of its success in the improvement of symptoms is the required amount

of the training sessions. Two studies mentioned above took between 24 and 40 sessions, which were repeated twice a week as a result the studies expanded over 3 months (van der Kolk et al., 2015; Gapen et al., 2016). Thus, patients might drop out as in case of Gapen and colleagues' study (2016) 26% of the patients dropped out. Another study found that a single session of EEG neurofeedback was sufficient to enhance salience- and default mode networks (Kluetsch et al., 2014), nevertheless authors concluded that there is a need for a study with repeated applications of neurofeedback. Another shortfall of the EEG neurofeedback is the lack of localization of neurofeedback due to the nature of EEG signal. The aim of EEG neurofeedback may be changing the amplitude of a wave, altering the synchrony between chosen electrodes (Reiter et al., 2016). Under these circumstances, it is not possible to target a specific region as rACC with EEG neurofeedback.

Another neurofeedback method is real-time functional resonance imaging (rt-fMRI) neurofeedback, where participants receive information on blood-oxygen-level-dependent (BOLD) signal of a selected region. With rt-fMRI neurofeedback one can learn to modulate a specific brain region activity in shorter time period. Birbaumer and colleagues (2013) explains this time difference based on the fact that brain is able to screen its vascular system which is producing the BOLD response, but it does not have a sensor for neuroelectric activity and authors argued that rt-fMRI neurofeedback enables faster 'sharpening' of the self-regulation of the brain activity. Even though rt-fMRI is a new method, it attracted a great deal of attention (for review see Thibault et al., 2018) and it became the new hope for psychophysiological treatments (Sitaram et al., 2007).

There are so far five rt-fMRI neurofeedback studies with PTSD patients and four of them targeted amygdala (Gerin et al., 2016; Nicholson et al., 2017; Misaki et al., 2018; Zotev et al.,

2018), one of them targeted ACC (Zweerings et al., 2018). The first study (Gerin et al., 2016) did not report the ability of amygdala downregulation, nevertheless a decrease in PTSD symptoms and normalization of resting state brain connectivity were found. The second study (Nicholson et al., 2017) revealed that PTSD patients were able to downregulate their amygdala while viewing personalized trauma words. The third study (Zotev et al., 2018) found that PTSD patients could upregulate their amygdala during happy emotion induction task. The last amygdala targeting rt-fMRI neurofeedback study (Misaki et al., 2018) used the same method as the third study and authors observed changes in functional connectivity of amygdala, somatomotor areas, ACC, insula, precuneus, and prefrontal regions as a result of amygdala upregulation. The only rt-fMRI neurofeedback of ACC study (Zweerings et al.,2018) showed that PTSD patients were able to upregulate their ACC, just slightly worse than healthy controls, but still the patients use more regions than healthy controls to compensate. In this study, 1 male, 8 female PTSD patients and 9 matching healthy controls were recruited to be trained in 9 sessions. Francati and colleagues' review (Francati et al., 2007) points to the importance of distinguishing the between trauma types and sexes.

In the current study we investigated the possibility to train female PTSD patients and healthy controls to regulate their ACC in a bigger sample (16 participants in each group) in only one session. We expected to find more activity during neurofeedback in PTSD group in comparison with control group as reported by Zweerings and colleagues (2018), but also different networks recruitment. We hypothesized that there would be an influence on the PTSD related network including amygdala in PTSD group as a result of successful training.

2.2.3 METHODS

Details about the stimulus, study design, image acquisition, data analysis can be found in Demircapa's article (Manuscript in preparation).

2.2.3.1 Participants

Nineteen healthy female and eighteen female volunteers with PTSD in total thirty-seven volunteers participated in our study. Two control subjects and a PTSD subject had to be excluded, as no target area could be determined in the localizer run ("non responder"). Another female was discarded due to an incomplete dataset and another PTSD patient was discarded as she had a vision problem, which prevented her to see the vısual stımuli. The remaining subjects, sixteen healthy female volunteers ranging in age from 21 to 33 (mean age = 25,56) and sixteen female volunteers with PTSD ranging in age from 21 to 49 (mean age = 32,62) with PTSD diagnosis. The control group had no history of neurological or psychiatric illness, head trauma, or psychoactive substance abuse and no MRI contraindications. They were recruited from Ludwig-Maximilian University graduate students and paid 25€ each for participation. The patient group was recruited from Klinikum rechts der Isar – Clinic for Psychosomatic Medicine and Psychotherapy and München Klinik Harlaching – Clinic for Psychosomatic Medicine and Psychotherapy and they were not paid for participation in line with the ethics regulation of Ludwig Maximilans University.

The study protocol was approved by the ethics committee of Ludwig Maximilans University and written informed consent was obtained from all subjects.

2.2.3.2 Stimulus

2.2.3.2.1 Functional localizer

In order to localize rostral ACC for neurofeedback, a functional localizer consisting of 16 black and white pictures of the faces of 8 individuals (4 men, 4 women) expressing happy and fearful emotions from Ekman and Friesen (1975) were presented in a block design.

The faces were arranged by expression type and gender into 4 sequences (Figure 1a and 1b), each lasted 40 s. The same expression from both gender added up to create stimulus block. A black star on a grey background (Figure 1c) was used as the low-level fixation block and it served as baseline. Five baseline blocks (40s) and four stimulus blocks (80s) constituted the localizer run, which took in total 6min 40s (Figure 2).

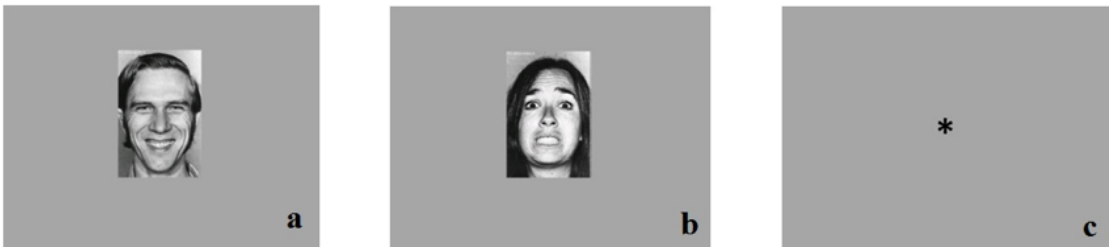

Figure 1. Stimuli in localizer. **1a** a male face of happy expression, **1b** a female face of fearful expression, **1c** low-level fixation screen. (Adapted from Demircapa, 2012)

The instruction 'Please attend and pay attention to facial stimuli and the related emotion. During the star, please stay fixated and try to minimize your thoughts' was presented on the screen prior the beginning of the run.

After the localizer, a resting state run was scheduled, in the meantime a radiologist and a neuro-cognitive psychologist agreed on the target area in the ACC for creating the functional ROI. The brain area with the highest contrast for emotion (happy and fearful faces pooled together) versus low-level fixation in the rACC was set as ROI. In case of no activation in the

rACC, the ROI was set in the adjacent ventromedial cortex, if possible (4 PTSD patients). No strict regulation of size and shape was imposed.

The same run repeated after the neurofeedback runs in order to investigate the impact of the neurofeedback training on the brain activation.

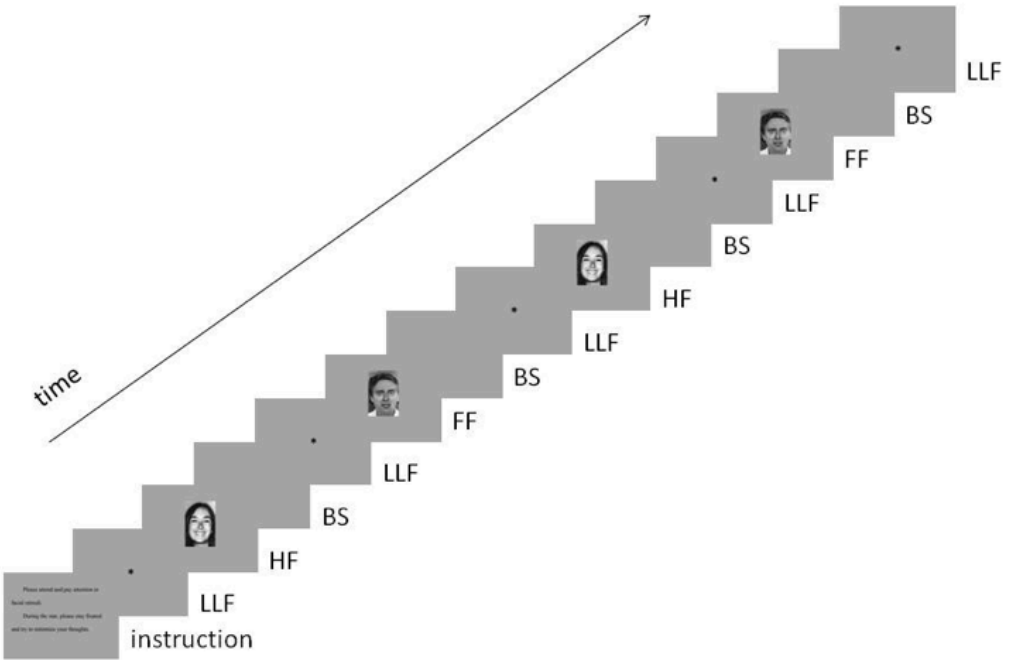

Figure 2. Experimental design. LLF = low-level fixation, HF = happy face, BS = blank screen, FF = fearful face. Localizer run starts with instruction for 10 seconds. Low-level fixation is followed by female and male happy faces. Second low-level fixation is followed by fearful faces. This sequence has been repeated one more time. Finally, localization run ends with a low-level fixation block. (Adapted from Demircapa, 2012)

2.2.3.2.2 Neurofeedback

Subjects had 4 runs to learn to regulate the activation in rACC. The feedback was consisted of ten squares and a bar, which were presented continuously throughout the run (Figure 3). On top of the visual feedback the subject was informed about her performance during the brakes between the neurofeedback runs. Each run was composed of 5 downregulation and 4 upregulation blocks and each block took 40 seconds. The subjects were informed about each upcoming run visually and verbally via their headphones.

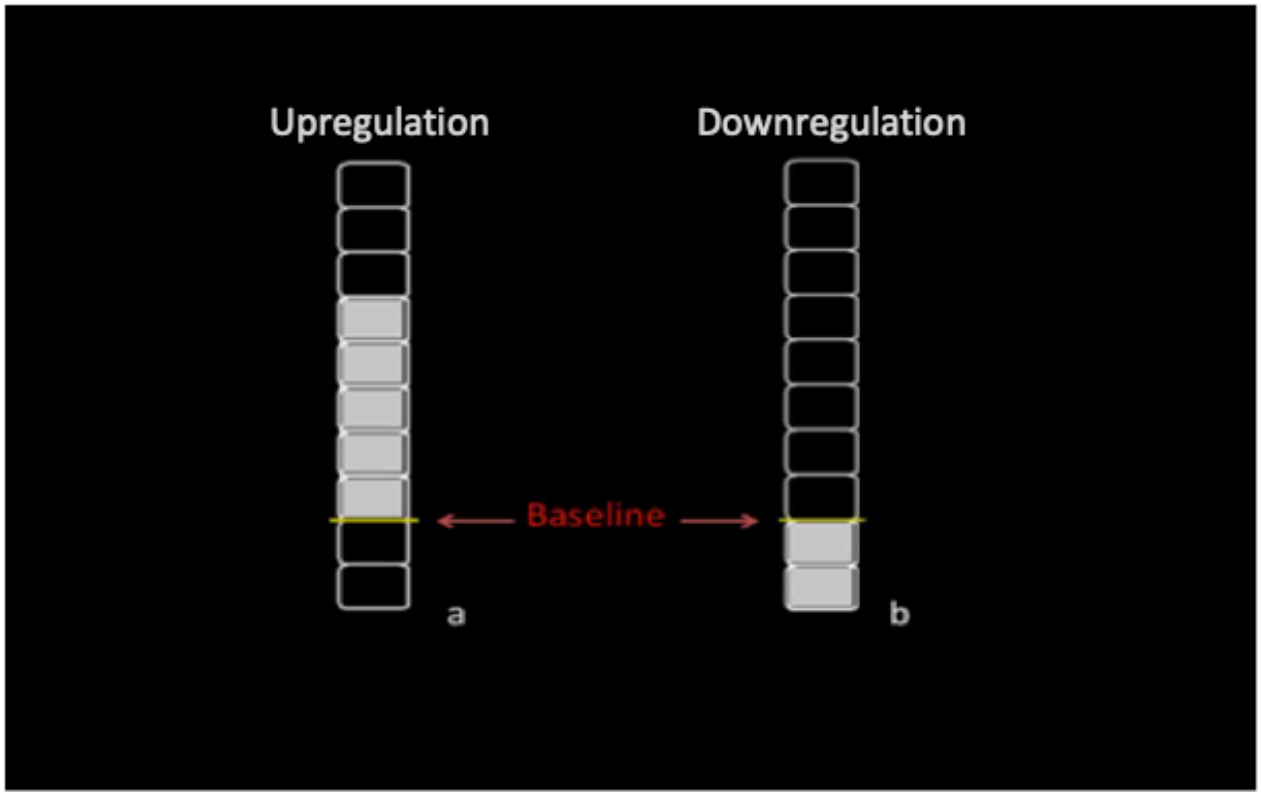

Figure 3. Feedback exemplars. **3a** the bar when subject succeeds an activation of ACC over the baseline. **3b** the bar when subject has an activation of ACC under the baseline. (Adapted from Demircapa, 2012)

Subjects were informed about the region of interest's function and they were set free to find a working strategy to upregulate the activity during the upregulation blocks and to reduce

the activity during the downregulation blocks. As a recommendation they were informed that positive emotional memories and meditative state might be helpful to achieve upregulation and downregulation respectively. Subjects were instructed to change strategies to find the best one during the first 2 runs and to try to expertise the strategy during the last 2 runs. They were informed about the BOLD signal's behavior.

2.2.3.3 Study design

First, participants were informed about the study in general and about the technique of neurofeedback and, the role of the ACC in detail including standardized strategy instructions explained below. Afterwards, they were asked to fill in questionnaires about demographics, health scanning questionnaire, verbal-linguistic intelligence test (WST, Aschenbrenner, Tucha, & Lange, 2000), and State-Trait Anxiety Inventory - A-State scales (STAI form 1, Laux et al., 1981). Then, subjects were carefully prepared for (f)MRI measurements including the accurate positioning and fixation of their heads in the head coil for minimizing motion artifacts.

Functional imaging was performed in the following sequence order: (1) localizer run (determination of the functional ROI), (2) 1st resting state sequence, (3) four neurofeedback runs, (4) localizer control run (5) 2nd resting state sequence. Lastly, the anatomical scan was acquired. After scanning, the participants received a questionnaire about rating the pictures of Beckman faces, Emotion Regulation Questionnaire (ERQ, Abler & Kessler, 2009), scales of emotional experience (Skalen zum Erleben von Emotionen - SEE, Behr & Becker, 2004), State-Trait Anxiety Inventory - A-Trait scales (STAI form 2, Laux et al., 1981), and Beck Depression Inventory (BDI, Hautzinger et al., 1994) to fill in them at home and post them back in two weeks.

2.2.3.4 Image acquisition

Subjects were scanned in a 3 T whole body system (Phillips ACHIEVA/INGENIA 3T), equipped with a standard 32-element head coil. Functional data were acquired using BOLD sensitive echo-planar imaging (EPI) with a T2*-weighted gradient-echo sequence in axial orientation. Functional images of the localizer runs and neurofeedback runs were obtained with the following parameters: field of view (FoV): 230 x 230 x 104 mm; voxel size: 3.0 x 3.0 x 4.0 mm^3; imaging matrix: 76 x 77; time of repetition (TR): 2000 ms; time of echo (TE): 35 ms; flip angle (FA): 90°; number of slices: 25; number of volumes: 265 (localizer runs); 185 (feedback runs); SENSE: 1,8 (p reduction, AP). Sequences covered the whole cerebrum. Slices were positioned parallel to the connection line between anterior commissure and posterior commissure.

A high-resolution T1-weighted three-dimensional sequence was acquired for anatomical reference. Slices were positioned in sagittal orientation using the following imaging parameters: FoV: 240 x 188 x 220 mm; voxel size: 1.0 x 1.0 x 1.0 mm^3; TR: 8.2 ms; TE: 3.7 ms; FA: 8°; number of slices: 220; SENSE: 2,5 (p reduction, AP)/ 2 (s reduction, RL).

2.2.3.5 Data Analysis

The performance of the participants varied in neurofeedback runs. Two rules were used to classify them according their performance as learners and non-learners: 1) Mean of beta values in 4 runs should exceed 0,1 in order to be analysed further as the participant is a learner. If not, the participant is classified as non-learner. 2) The participant's beta value difference between up & down should increase with each sequent run with the exception of 1 run (tiredness or attention distraction effect). In case that previous and sequent runs are both exceeding 0,25

beta value difference, this situation is not handled as decrease, since the participant is able control the area easily. The further analysis was done to compare healthy female and female PTSD groups, but also to find common activation for learners and non-learner (see Figure 4a and 4b).

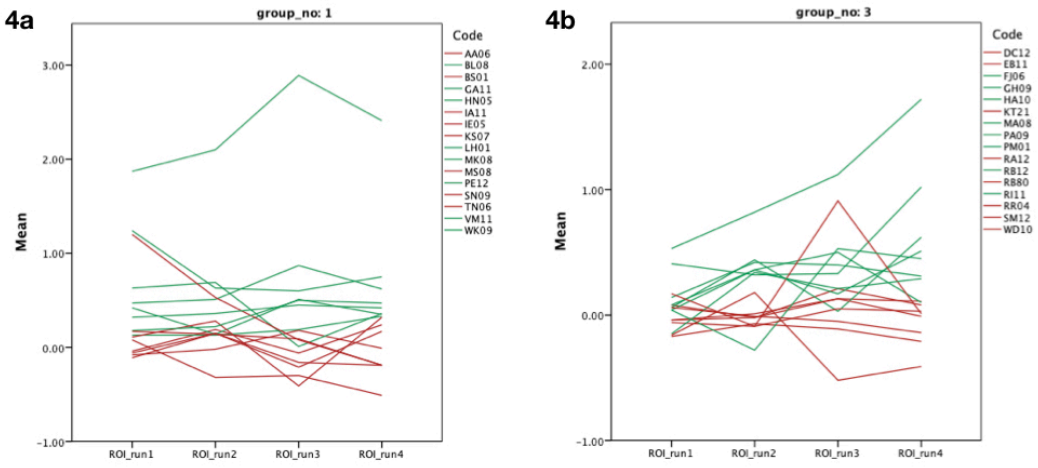

Figure 4. ROI activations, greens are learners and reds are non-learners **4a** beta values of ROIs of control group participants during neurofeedback runs. There were 8 learners and 8 non-learners **4b** beta values of ROIs of PTSD group participants during neurofeedback runs. There were 8 learners learners and 8 non-learners.

The online analysis was performed with Turbo Brain Voyager software package Version 3.0 (Brain Innovation B.V., Maastricht, the Netherlands). For the localizer run, the online GLM was computed using two predictors emotional faces and low-level fixation, convolved with a hemodynamic reference function. The threshold was 2.0 which is corresponding to uncorrected

0.05 significance level. For the neurofeedback runs, the online GLM was computed using one predictor for the regulation state either up or downregulation, convolved with a haemodynamic reference function. Only the highest activities in 33% of the voxels in the selected ROIs across three functional imaging slices were responsible for the neurofeedback signal.

The offline analysis was performed with the Statistical Parametric Mapping Software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). The first five volumes of each run were discarded due to T1 saturation effects. The remaining functional images were superimposed on 3D anatomical images. The complete data set was transformed into Talairach space through trilinear interpolation. Pre-processing of functional images was consisted of 3D motion correction, slice scan time correction, high pass temporal filtering (2 sines/cosines), and Boxcar predictors were convolved with canonical haemodynamic response function.

For the localizer runs, we ran 1 sample t-test by merging PTSD and control group together, conjunction analysis, contrasted PTSD and control groups, and also created learner and non-learner groups merging PTSD and control groups together. We compared happy, fearful, and resting blocks between pre- and post-neurofeedback localizers. For the neurofeedback runs we repeated the same tests and we compared upregulation and downregulation blocks. As two groups were significantly different from each other in age, age was added as regression in the group comparison.

Moreover, AAC mask from MarsBaR toolbox for SPM (Brett et al., 2002) and BA24s, BA25, BA32s, and BA33 masks (according to Palomero-Gallagher and colleagues' mapping of subgenual cortical areas (2015)) from Anatomy Toolbox for SPM (Eickhoff et al., 2005) were used for region of interest analysis. Then, activations were determined according to the clusters, which were automatically defined (minimum 20 voxels) by the software. Within each cluster of

statistical significance, the peak t-test value were determined and its location was expressed in x, y, and z coordinates. Additional a psychophysiological interaction (PPI) analysis between rACC and amygdala was performed by using SPM8.

The questionnaires are analyzed with Statistical Package for the Social Sciences (IBM, SPSS version 20.0). For bivariate relationships we used two-tailed Pearson's r. Independent two-tailed t-tests were used to compare group differences in questionnaires. Two-tailed paired sample t-tests were conducted to measure the effect of neurofeedback on selected ROIs from localizer runs.

2.2.4 RESULTS

2.2.4.1 FMRI results

2.2.4.1.1 Localizer

None of the tests mentioned in the methods revealed any significant supra threshold clusters at FWE 0.05 or uncorrected 0.001 levels.

2.2.4.1.2 Neurofeedback

First both groups are merged together in order to reveal the neurofeedback network. Upregulation and downregulation resulted in unique activation patterns (Table1 and Figure5).

Analysis	Location	Clusters size	x y z	z-statistics
up-down all	l V2	4572	-9.56 -53.57 5.35	5.41
	l insular cortex		-28.75 27.84 10.03	5.38
	l dlPFC		-23.38 37.42 27.25	5.21
	r V2	470	1.35 -87.95 10.38	5.28
	l V1		-4.11 -89.93 1.99	5.12
	r V2		-17.96 -78.68 2.83	3.31
down-up all	r Wernicke's area	716	48.43 -50.64 30.9	5.47
	r associative visual area		34.4 -68.12 37.14	4.97
	l Wernicke's area	711	-37.81 -65.21 38.9	4.69
	l visuomotor coordination area		-23.98 -71.13 41.27	4.29
	r visuomotor coord.	372	3.81 -62.89 42.53	4.38
	r dPCC		4.02 -33.9 34.47	3.99
	r FEF	50	45.79 16.19 39.92	4.09
	r premotor cortex		28.97 17.77 53.29	3.55
	r somatosensory cort.	30	45.61 -26.25 41.3	3.65
	r dPCC	23	1.1 -24.01 48.87	3.56
	l putamen	20	-28.93 -14.6 11.41	4.08
	l insular cortex		-31.8 -23.5 15.93	3.43

Table1. All participants Localizer peak voxel coordinates table (p<0.001; cluster size > 20 voxels)

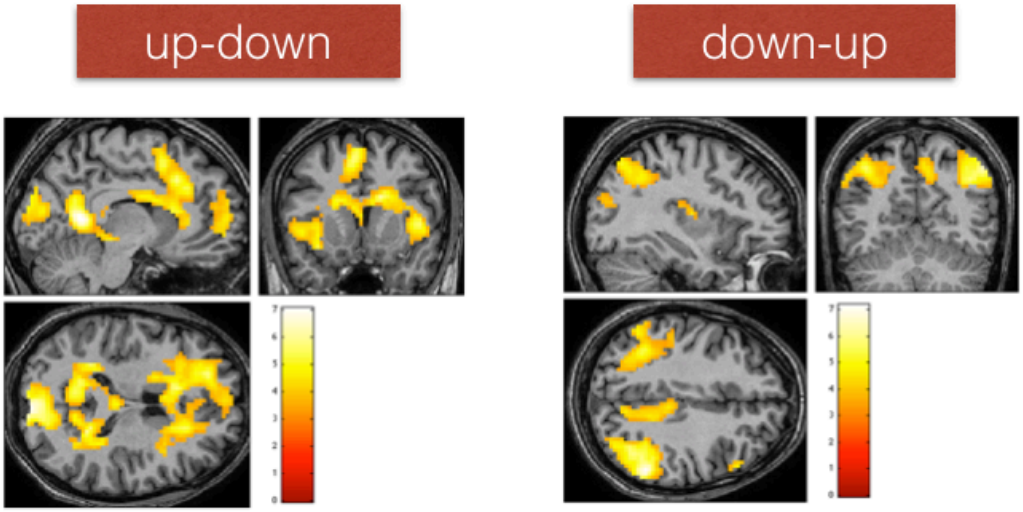

Figure5: All participants a) upregulation-downregulation activation in ACC, PFC and visual areas b) downregulation-upregulation activation in Wernicke's areas, association areas, and FEF (p<0.001)

A conjunction analysis was performed to understand which regions are most important for both PTSD and control groups. (see Table2 and Figure6).

Analysis	Location	Clusters size	x y z	z-statistics
up-down all	l insular cortex	66	-28.75 27.84 10.03	3.95
	l dACC		-20.41 33.39 10.7	3.88
	l retrosplenial CC	49	-9.56 -50.78 5.61	3.94
	l PCC		-17.92 -50.99 8.15	3.38
	l dlPFC	37	-23.38 37.42 27.25	3.97
	r V2	35	1.35 -87.95 10.38	4.01
	l V1&V2		-1.33 -89.95 2.04	3.61
	l premotor cortex	30	-4.43 0.91 53.84	3.54
	r PCC	22	18.18 -48.39 9.01	3.61
	l dACC	22	-12.42 22.61 34.14	3.40
	l caudate body		-12.27 15.53 19.95	3.35
down-up all	r Wernicke's area	69	48.43 -50.64 30.93	4.12
	r associative visual	24	34.41 -65.32 37.41	3.44

Table2. PTSD and control group conjunction analysis Neurofeedback peak voxel coordinates table (p<0.001; cluster size > 20 voxels)

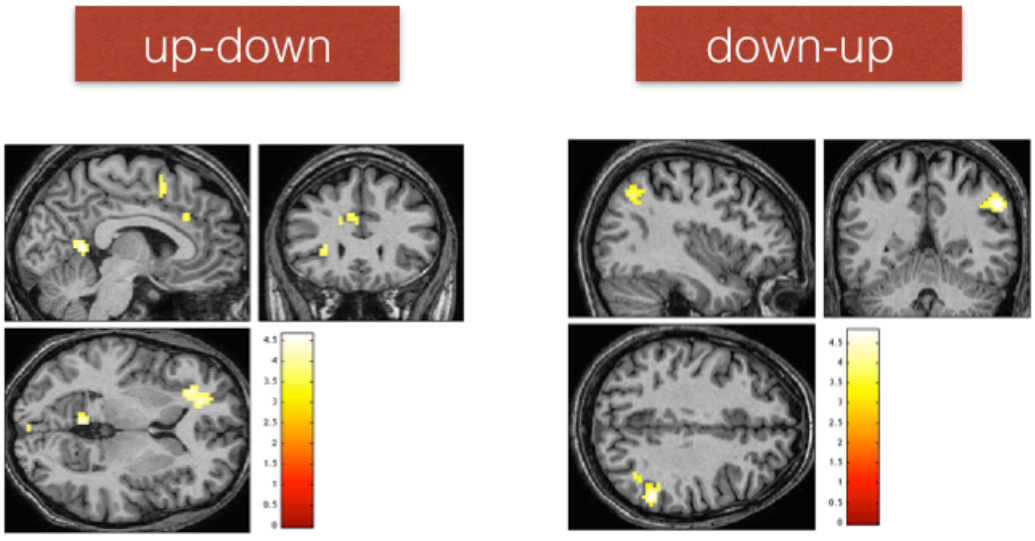

Figure2. Conjunction analysis for both groups (p<0.001)

A group comparison was performed by taking age as a covariate. Control group showed no activation in comparison with PTSD group, whereas PTSD group had more activated regions for both conditions when they were compared with control group (see Table3 and Figure 3).

Analysis	Location	Clusters size	x y z	z-statistics
female> PTSD				
upregulation all	no supra threshold clusters			
downregulation all	no supra threshold clusters			
PTSD >female				
upreg. all	l Wernicke	104	-32.17 -59.13 34.17	4.02
	l associative visual cort.		-32.23 -70.57 35.78	3.51
	r Wernicke	38	37.17 -57.21 40.92	4.08
	l premotor cortex	28	-34.8 -3.21 39.42	4.06
downreg. all	l premotor cortex	47	-37.58 -3.2 39.37	4.28
	r V1	28	23.58 -79.68 11.54	4.09
	r primary gustatory	22	57.09 -15.31 15.5	3.67
	r auditory cortex		57.07 -26.49 14.44	3.47

Table3. PTSD vs control group Upregulation and downregulation peak voxel coordinates table ($p<0.001$; cluster size>20 voxels)

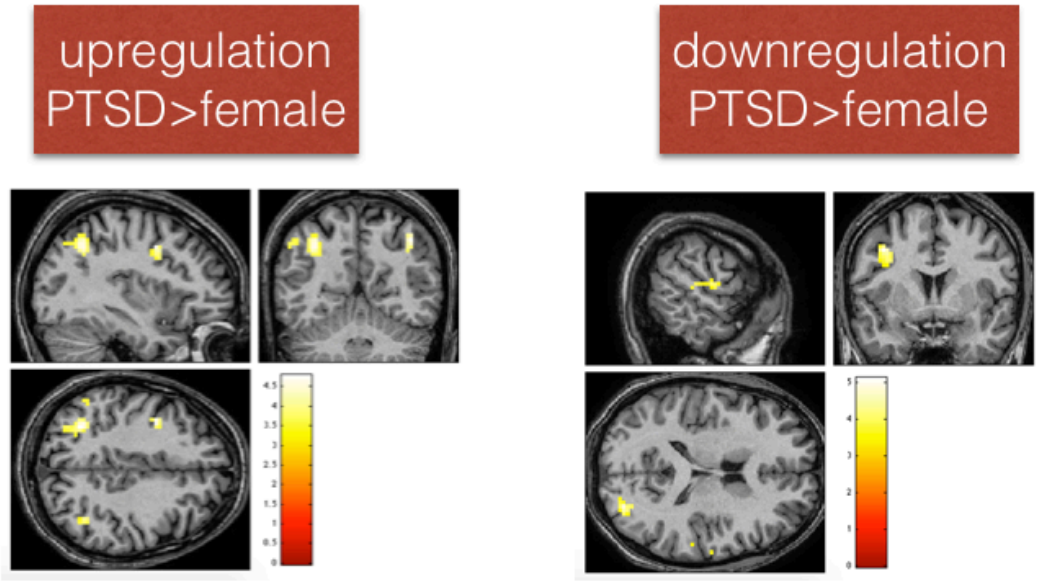

Figure3. PTSD vs control group a) upregulation b) downregulation ($p<0.001$)

PPI analysis did not reveal any coupling between amygdala and rACC for upregulation runs in comparison with downregulation when the data merged into one group and also when two groups are contrasted at FEW 0.05 or uncorrected 0.001 levels.

2.2.4.2 Post-scanning Interview

In the post-scanning interview, participants reported how well, they thought, they could regulate their ACC and also how they felt at the end of experiment in a scale from 1 (bad) to 5 (well). The mean for their impression how well they regulate their ACC was 3.34 (SD = 1). There was no group difference between PTSD and control group participants ($t=1.62$, $p>.05$). The mean for their feelings was 3.47 (SD =.88). No group difference was found ($t=-1.43$, $p>.05$). Control learner group (M=4.12, SD=.64) anticipated their performance insignificantly better than female non learner group (M=3.13, SD=1.25; $t(14)=2.02$; $p>.05$). The PTSD learner group (M=3, SD= .75) anticipated their performance slightly and insignificantly worse than non-learner group (M=3.12, SD=.99; $t=-.28$, $p>.05$). Subjects reported their strategies for upregulation and downregulation blocks. Subjects used mostly anticipation of happy memories, imagination of beloved ones, and/or performing their hobbies for the upregulation blocks and concentration on fMRI noise, on screen, and/or meditation for the downregulation blocks.

2.2.4.3 Relation of ACC Activity with Questionnaires

ACC activations (BA 24s, 25, 32s, and 33) measured by MarsBar and Anatomy Toolbox were correlated with questionnaires individually for both groups with the aim to predict whether the participant can benefit from the neurofeedback based on their questionnaires results.

Control groups' STAI1 results correlated with their ACC activity during upregulation runs (BA24s r=.589, p<.05; BA25 r=.617, p<.05; BA32s r=.671, p<.01; BA33 r=.639, p<.05). BDI had a negative correlation with control group's ACC activity during downregulation runs (B24s r=-.585, p<.05; BA25 r=-.658, p<.05; BA33 r=-.668, p<.05), but also during upregulation (BA25 r=-.581, p<.05). SEE self-control related questions revealed a negative correlation with ACC activity during both up- and down-regulation (BA24s upregulation r=-.581, p<.05; downregulation r=-.658, p<.05; BA33 upregulation r=-.533, p<.05; downregulation r=-.607, p<.05). Suppression results of ERQ showed negative correlation with control groups' ACC activity during downregulation.

Independent t-test for questionnaires revealed a significant difference between PTSD and control groups for ERQ reappraisal (t=-2.495, p<.05). Both groups differed from each other significantly in SEE acceptance, overwhelming, and absence (t=4.814, p<.001; t=-5.966, p<.001; t=-3.177, p<.001; respectively). PTSD patients scored higher in FDS as well as BDI (t=-6.116, p<.001; t=-7.066, p<.001; respectively). Expectedly control group scored lower in STAI1and STAI2 (t=-4.178, p<.001; t=-7.638, p<.001; respectively).

The correlation between the questionnaires and the ACC pointed out more differentiation between groups. PTSD patients ACC activation correlated negatively with SEE imagination (BA24s r=-.594, p<.05; BA33 r=-.547, p<.05) and correlated negatively with STAI1 (BA25 r=-.585, p<.05; BA33 r=-.553, p<.05) during downregulation.

2.2.5 DISCUSSION

In the current study we fed back the rACC activity, which was located by a functional localizer including emotional faces. We found that the half of the participants were able to

regulate their target region; there was no group difference. The upregulation led to the activation of neurofeedback related network (Emmert et al., 2016). PTSD group recruited more brain regions during up- and downregulation when contrasted with the control groups. Neurofeedback did not result in a detectable neural change in the second localizer run.

During the neurofeedback runs upregulation and downregulation resulted in a similar network as the meta-analysis revealed (Emmert et al., 2016). Emmert and colleagues (2016) located activations in insula, basal ganglia, posterior ACC, ventrolateral PFC, dlPFC and deactivations in PCC, precuneus, and bilateral transverse temporal area. They interpreted the results that insula activation pointed to the recruitment of interoceptive cognition and self-awareness networks and basal ganglia activation indicated the interception and motivation networks. The results of 1 sample t-test including the data from 32 participants revealed a wide activation encompassing the neurofeedback network and rACC and confirming Emmert's findings. We also performed a conjunction analysis in order to reveal the common network. This analysis disclosed dACC, insula, dlPFC, PCC, putamen, visual and motor cortex for the upregulation and Wernicke's area and associative visual cortex for downregulation. Both of the groups had same learning success and they also relied on the similar brain regions for the task.

We observed more activation during the neurofeedback runs in PTSD group in comparison to control group. Similar results were reported by Zweerings and colleagues (2018). These findings indicated that PTSD group was able to regulate their ACC as well as control group, but they needed to recruit more brain regions such as Wernicke's Area, associative visual cortex, and premotor cortex for upregulation and premotor cortex, primary visual, primary gustatory, and auditory cortex for downregulation. In conclusion, PTSD group had more multi-sensory activation during the neurofeedback runs. Simeon and colleagues (2000) have reported

depersonalization leads functional abnormalities in sensory areas and many PTSD patients show depersonalization symptoms as well. Additionally Falconer and colleagues (2008) found increased sensory areas' activation in PTSD group during an inhibition task in comparison to healthy controls. Increased multi-sensory activation was a PTSD specific pattern during the neurofeedback runs.

We failed to find any group differences for localizer runs. The patients were recruited from the trauma department of two hospitals and they were all taking medications and they were also attending psychotherapies. These interventions might have led to normalization of the neural activity. This might be due to habituation effect, which has been observed in rACC (Phan et al., 2003). However we found significant group differences between PTSD and control group related to the neurofeedback.

We did not find any changes in connection between ACC and amygdala for both of the groups and for both localizer and neurofeedback runs. PPI analysis requires a change of activity in both of the regions of interest in order to reveal a connection. The emotional faces were expected to increase amygdala activation in PTSD group as it is already reported in the literature (Shin et al., 2005). However this lack of the connectivity might be related to the PTSD group who was already receiving treatment. Diffusion tensor imaging might be the next step to overcome functional dependency and to measure the structural connectivity.

Half of the both of control and PTSD groups were able to learn to regulate their rACC independent of their group. This is promising, as the PTSD GROUP did not show any handicap to learn. Nevertheless the other half of the participants did not learn to control their brain activity. The correlations between the ACC activity and questionnaires revealed some insights about how to predict who would benefit from the training. Only STAI1 turned out to be significant for both

groups. Interestingly having higher STAI1 results in control group correlated with higher ACC activation during upregulation, whereas having high STAI1 results in PTSD group correlated with a better downregulation. One important point was that PTSD group had significantly higher results in STAI1 in comparison with control group. Hence, having slight anxiety seemed to be supporting the performance, while having high anxiety led to the inactivity of ACC. Simmons and colleagues (2008) demonstrated that high anxiety group had attenuated ventral ACC activity when compared to low anxiety group. Nevertheless there is a need to find better predictive factors about who would benefit from the rt-fMRI neurofeedback. As next step the predictive factors needs to be further investigated.

Even though 50% of the participants were classified as learner, it should be noted that this study included only one session in order to investigate the possibility to regulate the ACC in only one session. Other PTSD rt-fMRI neurofeedback studies included multiple sessions except two studies training amygdala (1 session: Gerin et al., 2016; Nicholson et al., 2017; 3 sessions: Misaki et al., 2018; Zotev et al., 2018; 9 sessions: Zweerings et al., 2018) and Gerin and colleagues failed to find any training success as a result of single session. The impact of multiple sessions in ACC training might be further explored. However another study used rt-fMRI to personalize the cognitive behavioral therapy strategies and the authors found that a single session resulted in a lasting impact (MacDuffie et al., 2018). A future research might focus on integration of the strategies in the therapy and measuring longer-term results.

PTSD patients use a variety of emotion regulation techniques such as numbing, detachment, and dissociation as different as different styles of expressive suppression, but they also rely on the cognitive reappraisal. Eftekhari and colleagues (2009) demonstrated that the ability to apply different emotion regulation strategies is an indicator of the psychopathology

severity. These findings highlighted the importance of constructive emotion regulation. Rt-fMRI neurofeedback provides PTSD patients a new tool to regulate their emotions. It enables them to review how their brains react to specific strategies. At the end of experiment many PTSD patients reported that they found the experiment extremely interesting, as they were able to observe their neural response to different strategies they tried out during the experiment. They also mentioned they might try to integrate these strategies in their daily life. As discussed above further investigation is needed for the integration.

There were multiple limitations in the current study. The most prominent limitation was that patients were already enrolled in treatment. Next step would be recruiting patients from waiting list to be able to attribute observed changes only to neurofeedback. Second limitation was the lack of no-neurofeedback group. This study focused on the implementation of the rt-fMRI neurofeedback of ACC. Further research should include no neurofeedback to assess placebo effect. Another limitation in the current study was gender. As Francati and colleagues (2007) stated there are big differences in neural activity of male and female PTSD patients. Demircapa and colleagues (Manuscript in preparation) found a gender difference in the ability to learn to regulate one's own neural activity depending on gender in healthy population. Based on these findings we decided to investigate ACC rt-fMRI neurofeedback with female PTSD patients only, but the future research should include male PTSD patients in order to generalize the findings for PTSD population.

Despite these limitations, the results of this study showed that PTSD patients might benefit from rACC rt-fMRI neurofeedback and it can be used to support ongoing treatments especially in treatment-resistant cases in order to approximate abnormal activity to normal or to 'more likely to benefit from the therapy' state. Nevertheless there is a need for further

investigation to predict the learner group. It should be also tested with male PTSD group to generalize the findings to PTSD group.

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3 General Discussion

The work described here focused on establishing a paradigm to upregulate rACC activity and implement it for PTSD patients in order to make a change in their abnormal neural activities. The first project was designed to establish a paradigm to localize emotional subdivision of ACC by viewing pictures of emotional faces and upregulate the target region. The second project aimed to implement the established paradigm with PTSD group. In this section the main findings and their implications will be discussed and future steps will be suggested.

3.1 Neurofeedback

The project focused to create a new tool to support PTSD treatment, as PTSD is a common psychiatric disorder (Kessler et al., 2005) with a big impact on the patients' lives (Warshaw et al., 1993), yet the recovery rates are still very low (Stein et al., 2006; Bradley et al., 2008).

Rt-fMRI neurofeedback attracted a great deal of attention since the first publication in 2003 (Weiskopf et al., 2003). It inspired many researchers to apply it to different incidents. Nevertheless, it was welcomed most enthusiastically by the clinical researchers with the hope to help patients.

The main motivation of the project was to apply rt-fMRI neurofeedback with PTSD patients in order normalize their brain activity. Our literature review led us to conclude that rostral ACC would be the right place to target, as it was identified to be the gate to the amygdala (Hamner et al., 1999) and recovery from PTSD correlates with the increased activation of rACC (Felmingham et al., 2007).

When the rt-fMRI neurofeedback was tested with the healthy population, we came across with an interesting fact that everyone did not learn to regulate their target area at the same speed and gender seemed to play a role in this situation. This was a surprising point for us, since

many articles did not even report the learner non-learner ratios. The target area was related to emotion regulation and the literature pointed to the gender difference in this field especially in rACC activity (Sacher et al., 2013).

We planned to limit our PTSD study to only one sex as researchers pointed to the differentiation in neural activity between the sexes (Francati et al., 2007). However, our findings from the first project convinced us further that we should focus to only one sex in the second study, namely female PTSD patients.

Unfortunately we were not able to find a change in the neural activity as a result of neurofeedback. Nevertheless the half of the participants did not learn to regulate their target region and as a result the group size might be too small in order to find a significant result. There is a need for replication of the study with a bigger group.

We also failed to find a predictor factor about the success of the learning across groups. Our questionnaires covered a wide range of emotion regulation and anxiety tests. However the predictive factor might be relying on the different factors. After revealing the mystery behind the unreported ratio of learners, there is a need for follow up studies in order to find the predictive factors. As we formulated previously, gaining control over the activation of a specific brain region might be a form of learning. Hence IQ might be a factor, which can be studied further in the future. Most of the participants in published studies are recruited from the universities. As a result the participants are highly educated and open to learning. Nevertheless our first project also included university students. In conclusion, we encourage researchers in rt-fMRI neurofeedback field to explore the underlyıng reasons.

Previous research demonstrated that the elevated ACC/mPFC activation was found to be increasing resiliency to develop PTSD (Osuch et al., 2008). Rt-fMRI neurofeedback can be used

after going through any traumatic event in order to increase the activity in rACC. This would allow the clinicians to protect the trauma survivors against the PTSD, which would save money as a result and more importantly improve the quality of life of the trauma survivors. Therefore, rt-fMRI is particularly suited for prevention.

3.2 Conclusions

We expect that rt-fMRI neurofeedback will play a significant role in the clinical settings. It provides an opportunity to normalize the abnormal activity in a target region. Thanks to the neuroimaging neural markers for different psychiatric disorders have been identified and rt-fMRI neurofeedback enables the researchers to target these regions without any medications and any side effects. The rt-fMRI does not aim to substitute the conventional methods. But the conventional methods do not seem to be working for many patients. This new tool might be helpful to approximate the abnormal activity to normal and as a result patients can benefit from the conventional methods better. The research showed that activation of specific region might be a predictor of therapy success (Bryant et al., 2008) and rt-fMRI neurofeedback might give the boost to the brain to be able to benefit from the conventional methods.

We implemented this new tool for PTSD patients and the patients tolerated the new method well. Moreover they reported that they enjoyed being able to see what was happening in their brain when they attempted to regulate their rACC. The method is not ready to be applied to all PTSD population yet. There is a need for further investigation of the predictive factors.

3.3 Future Steps

Despite the increasing number of research articles in rt-fMRI neurofeedback, the learner and non-learner groups are mostly ignored. Many articles did not even report the number of learners. First, there is a need for golden standards to define learner and non-learner groups. After the definition is accepted, it needs to be applied by rt-fMRI neurofeedback society. Second, the predictor factors should be examined. As mentioned above, we were unable to find a consistent predictor factor for learning. Future studies should investigate this in order to save time and money.

Another future step is to investigate the gender difference in rt-fMRI. In the first project we found a gender difference between the male and female groups. A more detailed investigation would reveal whether this difference is specific to emotion related task or to rt-fMRI neurofeedback.

Rt-fMRI neurofeedback is not a tool, which tries to substitute conventional treatment techniques; rather it aims to support them, especially in treatment-resistant cases in order to normalize the abnormal neural activity. One of the best ways to apply the rt-fMRI neurofeedback is to use the methodology to support ongoing treatment as MacDuffie and colleagues (2018) demonstrated. The future studies should test rt-fMRI neurofeedback as a supportive tool to treatment with PTSD patients.

Finally, rt-fMRI neurofeedback might be used as a prevention tool for PTSD by applying it just after the traumatic event. Currently used secondary prevention methods are psychological debriefing, pharmacological, and psychosocial interventions (Kearns et al., 2012). However, studies demonstrated that having elevated ACC activity creates resiliency against PTSD (Osuch

et al., 2008). Recently traumatized subjects might be trained to upregulate their rACC in order to prevent developing PTSD.

3.4 References

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Appendix

Abbrevations

Anterior cingulate cortex (ACC)

Attention Deficit Hyperactivity Disorder (ADHD)

Blood-oxygen-level-dependent (BOLD)

Brain-computer interference (BCI)

Brodmann Area (BA)

Cognitive behavioral therapy (CBT)

Electroencephalogram (EEG)

Functional near-infrared spectroscopy (fNIRS)

Functional magnetic resonance imaging (fMRI)

Electrocorticography (ECoG)

Magnetoencephalography (MEG)

Medial prefrontal cortex (mPFC)

Orbitofrontal cortex (OFC)

Post-Traumatic Stress Disorder (PTSD)

Posterior cingulate cortex (PCC)

Prefrontal Cortex (PFC)

Psychophysiological interaction (PPI)

Real-time functional magnetic resonance imaging (rt-fMRI)

Rostral anterior cingulate cortex (rACC)

Subcallosal cortex (SG)

Turbo Brain Voyager (TBV)

Ventromedial prefrontal cortex (vmPFC)

Acknowledgments

I want to thank to all people in my life who supported me until this point. It has been a long journey, but definitely a beautiful one!

I want to start with Kristina. She gave me the opportunity to explore the answers where I have been asking questions. Real time fMRI neurofeedback has been fascinating me since 2008 and I had the chance to run my own experiment in the most interesting field.

I want to thank Afra from my bottom of my heart as she kept answering my all questions and gave me the opportunity to be surrounded by many bright people at TUM.

Thank you GSN! I always felt supported and stimulated. I learned so much during this journey that I could not even imagine in the first place. I also met so many wonderful people through GSN who will be my life long friends. I appreciate every moment I spent as a GSN student. It has been a privilege.

Special thanks to Ebru, Efsun, and Kasia: I am not sure whether I would be still sane without you.

Last but not least, I want to thank to my family: without their love and support I could never make it to the end. My parents, especially my mother, nurtured my love for academia. My beloved husband Hayri supported me all the time, even I could not be with him because of my love for the research. Your trust in me, your love, and your motivation kept me writing and finalizing my thesis.

Publications

Silveira, S., Graupmann, V., Agthe, M., Gutyrchik, E., Blautzik, J., **Demirçapa, I**., ... & Hennig-Fast, K. (2013). Existential neuroscience: effects of mortality salience on the neurocognitive processing of attractive opposite-sex faces. *Social cognitive and affective neuroscience*, *9*(10), 1601-1607.

Demircapa, I., Paolini, M., (2016). Oltrogge, C., & Hennig-Fast, K. (Manuscript in progress). Gender differences in the ability to regulate rACC with real-time fMRI neurofeedback.

Demircapa, I., Paolini, M., Oltrogge, C., & Hennig-Fast, K. (Manuscript in progress). Real-Time fMRI neurofeedback of ACC with PTSD patients.

Declaration of author contributions

1. **Demircapa, I.**, Paolini, M., (2016). Oltrogge, C., & Hennig-Fast, K. (Manuscript in progress). Gender differences in the ability to regulate rACC with real-time fMRI neurofeedback. **Author contributions:** Study concept and design: I. D.,; data acquisition: I.D. M.P., C.O., data analysis: I.D, drafting the manuscript and figures: I.D., M.P., K.H.-F.

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2. **Demircapa, I.**, Paolini, M., Oltrogge, C., Schäflein, E., & Hennig-Fast, K. (Manuscript in progress). Real-Time fMRI neurofeedback of ACC with PTSD patients. **Author contributions:** Study concept and design: I. D., K.H.-F.; data acquisition: I.D. M.P., C.O., E.S. data analysis: I.D, drafting the manuscript and figures: I.D., M.P., K.H.-F..

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