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REVIEW ARTICLE

What fMRI can tell as about panic disorder: bridging the gap between neurobiology and psychotherapy

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Abstract

Fifty years ago, when the effect of antidepressants on panic disorder was described, a significant progress in understanding this anxiety disorder has been made. Theoretical mechanisms and models of fear and panic disorder were proposed and tested in animal models and humans. With growing possibilities of non-invasive neuroimaging techniques, there is an increasing amount of information on the panic disorder. Unfortunately, a number of circumstances lead to inconsistent findings and its interpretations. In our review, we focused on functional MRI in panic disorder, limitations of current studies, possible interpretations and proposals for future direction. In our opinion, the current findings support the neuroanatomical model of panic disorder at the level of group data analysis. But at the same time, the results suggest significant inter-individual differences across the patients, which may be related to each patient's individual history, woven into their neural network and affecting the individual symptoms and response to therapy.

INTRODUCTION

Panic disorder, according to the Diagnostic and statistical manual of mental disorders, is characterized by recurrent unexpected panic attacks, and anxiety about future panic attacks or their consequences, or a significant behavioral change because of the panic attacks (American Psychiatric Association 1994). Panic disorder is a frequently occurring anxiety disorder with a lifetime prevalence rate of 4.7% (Kessler *et al.* 2005). Panic disorder is associated with high levels of social, occupational, and physical disability, considerable economic costs (Wittchen *et al.* 2010; Goorden *et al.* 2014) and it is important to take into account the costs and treatment effectiveness of PD (Gould *et al.* 1995; Katon WJ *et al.* 2002; Katon *et al.* 2006). Pharmacological treatment of PD is considered to be effective, and it is often the treatment of choice (Jefferson 1997; Andrisano *et al.* 2013). Although cognitive therapy, exposure therapy, and cognitive-behavioral therapy (CBT) appear to be efficacious and efficient in the treatment of anxiety disorders (Otte 2011; Ougrin 2011), only a minority of patients has access the suitable psychotherapy. Combining drug treatment with CBT is the most successful treatment strategy for them (Bandelow *et al.* 2013). Despite advances in the

treatment of panic disorder, about 30% of the patients treated with standard procedures remain symptomatic (Black *et al.* 1993; Bandelow & Rüther 2004). In comparison with the patients selected in clinical studies, who are often less severely ill, younger, and have fewer co-morbid conditions, the percentage of chronic panic patients may be higher in the general clinical practice (Bandelow *et al.* 2004). To streamline and shorten treatment and reduce the disorders costs, researchers are looking for specific treatment response predictors. Six clinical variables are associated with high-risk poor outcome including panic severity, comorbid depression, the presence of agoraphobia, duration of illness, comorbid personality disorder and female sex (Pollack *et al.* 2000). Recent neuroscience approaches suggest that neural biomarkers could improve accuracy in treatment response prediction beyond demographic and clinical predictors (Ball *et al.* 2014), but there is a lack of studies focused on the neural biomarkers of therapeutic response in panic disorder. Interindividual variability of PD symptoms and treatment response is not understood and remains a challenge to the researchers.

Panic attacks are typically associated with experiencing unpleasant emotional states, sympathetic autonomic reaction and unpleasant physical symptoms, which have their neurobiological correlates. Fear, escape, avoidance behavior and panic-like responses are present throughout the animal kingdom. Building upon animal models of fear, Gorman proposed and later revised a complex neuroanatomical model of panic disorder. His model explained the role of the brainstem, limbic system, prefrontal cortex and the theoretical pathways mediating the influence of prefrontal areas in the limbic system in panic disorder (Gorman *et al.* 1989, 2000, 2004). From the neurotransmitter perspective, a pivotal role in maintaining the balance of anxiety circuits is played by the serotonergic, noradrenergic and GABAergic systems, and other chemical mediators that are supposed to have a role in homeostasis of anxiety circuits (Coplan & Lydiard 1998). Under the influence of Gorman's and other derived models, many hypotheses focused on different aspects of panic disorder have been tested so far.

In recent decades, there is growing importance of non-invasive brain imaging techniques that offer new information on the nature of PD. Unfortunately, the reported differences in multiple domains between healthy controls and patients with panic disorder are inconsistent across the methods and patient samples. Morphological neuroimaging studies repeatedly confirmed the presence of structural changes in specific brain regions associated with anxiety control in panic disorder patients (Bremner 2004; Ferrari *et al.* 2008; Del Casale *et al.* 2013). Morphological, metabolic, neurotransmitter, receptors and functional changes in neuroimaging methods have been described (Dresler *et al.* 2013) in the context of neuroanatomical hypothesis and CBT (de Carvalho *et al.* 2010). Findings support the role of brain structures such as the prefrontal cortex, the anterior cingulate cortex and limbic areas (hippocampus and amygdala) in the panic response. In a few recent years, research has been focused on the treatment response and its prediction using fMRI technics.

METHODS OF THE LITERATURE REVIEW

A comprehensive literature search was conducted using Medline/PubMed and Web of Science to identify neuroimaging studies on the panic disorder (Status: January 2015). Search terms comprised "functional magnetic resonance imaging" (fMRI) and "panic disorder". Only the original English studies on the fMRI BOLD (blood-oxygen-level dependent) and panic disorder were included. Articles regarding focal brain lesions, epilepsy, exploring hypotheses in healthy individuals, or studies in which the PD findings were not separated from other investigated anxiety disorders were excluded. Original papers were divided into several categories according to the focus of the study, used stimuli or individual aspects of the panic disorder and its treatment.

SPONTANEOUS PANIC ATTACKS IN THE SCANNER

In the first published case study, a patient was included in the research focusing on auditory habituation in emotionally neutral sounds. Increased activity in the right amygdala (parahippocampal gyrus) and right putamen was observed during the spontaneous panic attack which occurred (Pfleiderer *et al.* 2007).

Second, a woman with restless legs syndrome, during resting state fMRI data collection, developed her first panic attack. Heart rate was positively correlated with the activity in the left amygdala, negatively correlated in left middle temporal gyrus, a positive trend was observed in the right amygdala and left insula, in left insula also manifested increased activity during the attack (Spiegelhalder *et al.* 2009).

The third article describes two patients, who developed panic attacks while watching emotional faces. Patient B, in the ROI analysis deactivated in the right DLPFC. Patient A has activated the right amygdala and the insula bilaterally, increasingly DLPFC at the beginning and decreasingly DLPFC at the end of the attack (Dresler *et al.* 2011).

To summarize, these rare findings confirm the involvement of amygdala and insula in a panic attack.

COGNITIVE AND OTHER ALTERATIONS IN PD

In the first study of this group, a complex motor paradigm for the non-dominant arm in a woman was performed by patients and controls. Motor task has been rehearsed in advance and instructions were visualized. The patient displayed an increased activity in the right temporal and occipital lobe (BA19 and BA39) and

decreased activity in the putamen bilaterally (Marchand *et al.* 2009).

Patients in remission and controls were asked to evaluate the emotional faces with congruent and incongruent textual accompaniment as quickly and accurately as they can. In the emotions, the evaluation was slower in the patients, without affecting accuracy. Depending on the pair-wise contrasts used, the groups differed in the dorsal ACC, DLPFC, other prefrontal, parietal and temporal areas, brainstem, amygdala and parahippocampal. During the task, patients were more influenced by the incongruence of the previous task. Regardless of causality, findings suggest that DLPFC dysfunction is present in remitted PD (Chechko *et al.* 2009).

In emotional Stroop test, where colored neutral or emotionally negative words were judged, the patients and controls activated similar brain regions. Comparison of emotional words with the neutral words showed greater differences in PD, mostly in the left hemisphere in the IFG and MFG, middle temporal gyrus, posterior cingulate cortex, the inferior temporal lobe and on the right side in the IFG and medial temporal gyrus. In group differences, patients increasingly activated only the left IFG. From a behavioral point of view, groups differed in reaction time, which was longer for the emotional words evaluated in PD (Dresler *et al.* 2012).

Spontaneous panic attacks have also been associated with false anxiety alarm and increased sensitivity to carbon dioxide levels in some brain regions. Patients in the respective study were exposed to an increasing concentration of the inspired CO_2, and they were strongly activated brainstem compared with controls and divers. In addition, activity in the right anterior insula correlated with the subjective feeling of respiratory distress (Goossens *et al.* 2014).

No difference between patients and controls showed a in the BOLD response. However, in pH-sensitive MRI window (T1R), was found a signal increase in the visual cortex and decrease in the right anterior cingulate in patients. The signal in left inferior parietal lobe and left middle temporal gyrus correlated positively with BAI, whereas in the right insula the negative correlation was found (Magnotta *et al.* 2014).

To summarize these studies, attentional bias in processing of disorder-specific stimuli was observed in symptomatic and also in remitted PD. Alterations in prefrontal (DLPF, MPC, IFG), temporal, parietal, and occipital, ACC, PCC, insula, amygdala, parahippocampal gyrus and brainstem showed in PD patients, suggest a complexity of relationship between the neural networks involved in cognitive tasks with emotional overtones.

FEAR CONDITIONING AND ITS ANTICIPATION

Anticipation unpleasant electrodermal stimulus among PD, PTSD and controls demonstrated group differences. Whether they will be in danger (electrical stimulus) or not, the subjects were informed in advance. PD patients showed significantly less activation in the threat condition and increased activity to the safe condition in the subgenual cingulate, ventral striatum and extended amygdala, as well as in midbrain periaquaeductal grey (Tuescher *et al.* 2011).

During differential fear conditioning (aversive audio signal) in PD, increased activity was detected in the IFG bilaterally and the right superior frontal gyrus, compared with controls. Simple conditioning and safety signal processing were related to increased midbrain activation in PD patients. During extinction, but not during the familiarization and acquisition, there was increased activity in patients in the left amygdala. The findings testify for altered top-down and bottom-up processing of fear conditioning and confirm the unclear role of the amygdala in PD (Lueken *et al.* 2014).

Altered top-down and bottom-up processing in fear conditioning was associated with reduced discrimination between safe and threatening stimulus linked to altered response in the midbrain, PFC and inconsistently in the amygdala. A functional MR finding suggests the easier establishment of conditional fear and its slower extinction in PD.

EMOTIONAL STIMULI – PROCESSING AND REGULATION

Patients compared with controls, showed reduced activation when were exposed to the fearful facial affect in cingulate cortex bilaterally and the right amygdala, but the opposite effect for happy faces and less for the neutral faces, were patients activated strongly in similar regions. The response in the left cingulate gyrus correlated with anxiety during exposure to fearful faces in patients. In some used contrasts, the group differences were found only in placing more active voxels within the brain structures (e.g., ACC). Instructions for the subjects of the investigation was not clearly described (Pillay *et al.* 2006, 2007).

Functional MRI response in patients to passively watched emotional faces showed differences between men and women. In women compared to men, all emotional faces activated the amygdala. Furthermore, angry and neutral emotional expressions activated strongly the right amygdala compared with a happy or anxious expressions and increased amygdala connectivity among other regions including the right DLPFC, in reaction to angry faces (Ohrmann *et al.* 2010).

Panic patients showed less activity in the left amygdala and right lingual gyrus while they were exposed to emotional faces, in comparison with controls. Anxiety severity scale (BAI) across the anxious subjects (social phobia, panic disorder and comorbid SP with PD) correlated positively with the functional connectivity of the left amygdala with right rostral ACC and left MPFC, while they were exposed to fearful > neutral faces. Par-

ticipants were instructed to indicate the actor's gender (Demenescu *et al.* 2013).

Patients with GAD, PD and controls exposed to a mixture of images and negative images, should evaluate their current negative emotions and maintain or reduce them. During the emotional regulation (reappraisal and maintenance) both GAD and PD patients, showed less activity in prefrontal areas than controls, in addition, the intensity of activation was inversely correlated with severity of anxiety and functional impairment (Ball *et al.* 2013).

Amygdala responses to masked and low spatial frequency (LSP) fearful faces showed that LSF stimuli did not elicit amygdala response across the subjects. Controls showed bilateral activation of the amygdala in response to fearful masked faces versus neutral faces, but patients failed to show activation within the amygdala. Anxiety during the investigation negatively correlated with left amygdala activity in patients. Findings suggest the presence of subliminal anxiety circuits in the general population and patients' poorer ability to recognize danger (Ottaviani *et al.* 2012).

When comparing the reactivity of PD patients (>controls) on masked faces, increased activation in the right parahippocampal and fusiform gyrus was observed. A reduction of activity in the left superior VMPFC and orbitofrontal cortex (Killgore *et al.* 2014) was found in the patients.

When the probands perceived neutral faces and places (instruction were not clearly described), the patients showed significantly less brain activity in the fusiform gyrus, the inferior occipital gyrus, the calcarine gyrus, the cerebellum, and the cuneus but not precuneus compared with the healthy controls (Petrowski *et al.* 2014).

When matching fearful and happy facial expressions in PD, GAD, SP and HC, greater differential right amygdala activation was related to greater negative affectivity across all anxiety disorders compared with controls. Increased activity in left dorsal insula was associated with PD compared with other anxiety disorders. Subjects were instructed to evaluate the emotions of viewed faces (Fonzo *et al.* 2015).

To summarize, facial expressions have signalization functions, recognizing their emotional valence can be important in identifying the threats. Usually less of activation differences in response to threatening compared with neutral facial expression, suggest a poorer ability to distinguish the safety and threats in patients. Increased amygdala-PFC connectivity while patients process a danger, may support a hypothesis that there is a positive feedback (dysregulation) between PFC and emotional structures in PD. The finding of less activity in prefrontal areas during the emotions control tasks, confirms the assumption of PFC dysfunction in PD. Positive or negative correlation of brain response to stimuli with anxiety scales suggests a particular role of the relevant structures in PD patients. Results indicate disturbed PFC and subcortical functions in PD. When we interpret the findings, it is necessary to bear in mind that the individual responses to emotional facial expressions are generally influenced by personality traits, and also by the participants' sex in PD patients. Unfortunately, the personality traits were not often assessed in the published studies and further, it seems that facial expressions are not specific stimuli for panic disorder.

PANIC DISORDER-SPECIFIC STIMULI IN fMRI

The imagery of individually highly distressing and neutral situations resulted in increased differences in the right parahippocampal gyrus, right IFG, anterior and posterior cingulate bilaterally in PD. Activation in the anterior cingulate was extended to MPFC, posterior cingulate and precuneus (Bystritsky *et al.* 2001).

When comparing threat-related and neutral words, there was increased activity in the left cingulate (BA 23 and 30), left DLPFC (BA 46) and right more than left parahippocampal asymmetry in patients compared with controls. Controls activated strongly in many brain areas, but the authors speculate about the possible hyperventilation consequences in patients. While listening, the subjects quietly assessed the emotional valence of the words (Maddock *et al.* 2003).

In the processing of anticipated agoraphobic stimuli, PD showed increased response in the right insula, precuneus bilaterally, parahippocampal gyrus and the angular gyrus. Anticipation itself leads to increases activity of the left amygdala and left insula. In addition, when PD patients were watching agoraphobic situations, a correlation between the HAMA (Hamilton Anxiety Scale) and both amygdala and parahippocampal activation and between MI (Mobility Inventory) and right insula was found (Wittmann *et al.* 2011).

During the anticipation of anxiety in patients compared with controls, an elevated response in ventral striatum was found bilaterally, in the left insula, but not in the amygdala. Left insular activity correlated with the MI (Mobility inventory) scale and activity in the ventral striatum correlated with the evaluation of anxiety that was related to agoraphobic stimuli during fMRI scanning. Consistently with the previous study, subjects were requested to experience the presented situation, and they were asked to pay attention to the cue and its predictive content before picture presentation (Wittmann *et al.* 2014).

To summarize, during processing of panic disorder-specific emotional stimuli, there were consistently increased responses or increased differences in responses to threatening compared to neutral stimuli in PD patients. Differences were more often shown in the anterior and posterior cingulate, parahippocampal gyrus, insula, precuneus and PFC, regions hypothesized to play a role in PD. BOLD response to specific stimuli in the insula, parahippocampal gyrus, amygdala

and striatum, correlated positively with anxiety scales, which suggests the role of these structures in PD. Insula may have a role in anticipation of danger, the role of the amygdala was not clearly established. Patients respond excessively to PD-specific stimuli in comparison with healthy controls.

FUNCTIONAL MRI AND GENETICS

Domschke *et al.* (2006, 2008) examined the impact of specific genetic variants in serotonin biology on processing of emotional stimuli in PD. Patients were divided into groups according to genetic parameters and exposed to emotional faces. Two alleles concerned the 5-HT_{1A} receptor: the 1019G allele is associated with anxiety and avoidance behavior 1019G whereas the 1019C allele predisposes to resilience ., Two others concerned the 5-HTT transporter: the short (S) allele is associated with higher risk compared to the long (L) variant. Comparing patients exposed to fearful (>neutral) faces and matching the risk for the 1019G homozygote with the better 1019C variant, showed decreased activity in the right VMPFC and OFC and cingulate cortex. Homozygotes for the G allele manifested higher activation in the left amygdala for happy facial expressions. Masked fear led to reducing activity in the right VMPFC for the G homozygote. In S allele carriers compared with the L allele, higher activity was observed in the right amygdala when exposed to happy faces. Participants had to focus their attention if they experienced a human face (Domschke *et al.* 2006).In the same group of patients and performing the same task, the authors investigated the role of the Val158Met catechol-O-methyltransferase (COMT) genotype on emotional face processing. The higher-risk GG homozygote (>AA homozygote) showed increased activation in the right amygdala for fearful faces. Increased activity in the left OFC and less deactivation in the left VMPFC has been detected in at least one risk G allele for frightened faces and deactivation in VMPFC bilaterally for happy faces. COMT variants did not differ in DLPFC response (Domschke *et al.* 2008).

To summarize, the reported samples of PD patients showed different response in OFC, VMPFC, cingulate and amygdala when exposed to emotional faces, according to their genetic parameters. These findings confirm the importance of genetic factors, known from previous clinical trials, and may explain a part of the individual endophenotype variance in PD.

TREATMENT RESPONSE TO PSYCHOTHERAPY AND ITS PREDICTION

Combining genetic traits (polymorphism of the promoter for 5-HT_{1A} receptor) with fear conditioning, behavior and the effect of CBT showed that risk genotype GG is associated with avoidance behavior during exposition treatment. During the early acquisition phase, at the beginning and end of CBT treatment, GG > CC was associated with increased activation in the amygdala, hippocampus, cerebellum, parietal and temporal areas. Whereas, CC > GG showed increased activity in the insula, cingulate cortex, middle parietal and occipital areas bilaterally. Activity in the bilateral amygdala correlated with the number of G alleles and right insula response correlated negatively with anxiety during exposure treatment (Straube *et al.* 2014).

Patients (> controls) showed increased difference for emotional (positive, negative) compared with neutral words in the SMA and reduced differences in the right PFC (VLPFC for negative and DLPFC for positive words). When comparing the nogo/go task for the same types of words, patients have increasingly activated the left amygdala and hippocampus for neutral words and the left caudate for negative words. Controls have activated strongly in left PFC (VLPFC, lateral OFC) for positive words. After a brief psychodynamic psychotherapy, in patients the fronto-limbic balance normalized (activation of the patients did not differ from controls). Participants were instructed to indicate the font style of projected words and were not informed about the different emotional valence of used words (Beutel *et al.* 2010).

The effect of CBT on fear conditioning combining a visual stimulus and an aversive audio sound was observed in patients compared with controls in the left IFG. Patients manifested reduced response to the conditioned stimulus after CBT treatment and the rate of decrease correlated with a reduction of agoraphobic symptoms. Furthermore, in the patients an increased functional connectivity between the left IFG and amygdala, hippocampus, anterior cingulate bilateral and lateral PFC appeared after CBT. Functional connectivity of the IFG negatively correlated with the severity of symptoms at the end of treatment. The study was a randomized, controlled, multicenter and the CBT treatment was standardized (Kircher *et al.* 2013).

In a post-hoc analysis of responders and non-responders to CBT during the fear conditioning (extinction), higher pretreatment difference between the threatening and safe stimulus was observed in responders. Responders compared to non-responders manifested stronger fMRI response in the right ACC, hippocampus, amygdala and leftward in the fusiform gyrus and middle temporal gyrus. Furthermore, increased functional connectivity among the right ACC and left amygdala before treatment was associated with a good response to CBT treatment in PD. Increased activity in the right hippocampus occurred in responders after CBT treatment (Lueken *et al.* 2013).

To predict rapid response to short CBT treatment, in another study, the patients were exposed to emotional and neutral visual stimuli. Patients were instructed to judge their negative emotions during the fMRI task, and to experience them or to try to alleviate them. A positive correlation between the right hippocampus

volume and improvements in the agoraphobic scale after CBT was found. Sufficient response (decrease in PDSS – panic disorder severity scale) to CBT correlated with response to threatening stimuli in the insula bilaterally. Increased activation of the left PFC, when experience (> alleviation) of emotions was compared, predicted a good response to treatment (Reinecke *et al.* 2014).

Another work predicts negative response to CBT in chronic PD. In this study, a post-hoc analysis showed increased activation in non-responders compared with responders in the bilateral DLPFC, left IFG, left frontal eye field, right parietal lobule and left amygdala before CBT. Furthermore, the correlation between functional MRI signal across those regions and post-treatment improvement was found. Patients were instructed to passively listen to the words and differences in response to threat-related words and neutral words were compared (Grambal *et al.* 2015).

Connectivity between ACC and the amygdala correlated with the frequency of the risky S-allele (promoter of the serotonin transporter 5-HTTLPR) only in responders. A significant interaction effect of genotype, negative functional ACC-amygdala connectivity and response to CBT was found only in the low-risk L/L genotype. Authors were aiming to compare the extinction phase of conditioned response that simulates exposure therapy of panic disorder (Lueken *et al.* 2015).

Another study examined the activity in dozens of morphologically defined regions of the brain during fear conditioning to predict individual response to CBT. Individual prediction of response to CBT can be determined with an accuracy of around 80%, sensitivity of about 90% and a specificity of about 70%, depending on the contrast type (Hahn *et al.* 2015). Another study that used the same method found the similar results, but PD and GAD patients were analyzed together (Ball *et al.* 2014).

To summarize this section, recent studiespresent growing evidence that fMRI can be sensitive enough to demonstrate the effect of therapy and its prediction. Better response to CBT is associated with a stronger reaction to threat-related stimuli and differentiation between safety and danger in limbic and cortical regions, with stronger cortico-limbic functional connectivity and prefrontal competencies during the emotional control. Non-responders respond more strongly during the fear conditioning and extinction phases, have difficulty to distinguish between safe and threat and there is evident prefrontal dysfunction. Genetic factors influence the endophenotype, behavior and treatment response to CBT. After psychotherapy, fronto-limbic balance improvement occurred. Typically, the findings describe the group trends in treatment prediction, but only one study predicts individual response with 80% accuracy. The above described differences between responders and non-responders open up new speculations and hypotheses for PD.

A BROADER PROPOSAL OF AN INTEGRATIVE PANIC DISORDER MODEL AND CBT TREATMENT RESPONSE IN THE LIGHT OF FMRI FINDINGS

Bearing in mind the diversity of fMRI studies and heterogeneity of the subjects, we decided to use the less specific model, which would be less misleading. We can regard as established that many cortical and subcortical structures and networks are involved in panic disorder circuits. Specific reactivity and inconsistent symptoms during panic attacks across the patients suggest that panic originates in an abnormally sensitive fear network (Gorman *et al.* 2000). Individual vulnerability and endophenotype may be understood as a consequence of the mutual interaction between the congenital factors, childhood formative influences and other life events (Gorman *et al.* 2004). When an overflow of individual stress buffering capacity combines with personal predisposition, the panic disorder appears.

At the neuroimaging level, local morphological, metabolic, neurotransmitter, receptors and functional changes have been described (Dresler *et al.* 2013), but little is known about the functional, efficient and dynamic connectivity further integrating the functional neuroimaging data. Group imaging analyses may help to understand the general characteristics of the prefrontal regions and emotional system relationship. When we look at cognitive abnormalities in PD, an explicit memory bias for physical threat words (Lundh *et al.* 1997), better episodic memory for threat-related words (Coles & Heimberg 2002), and disturbed processing of threat-related and negatively valenced words (Maidenberg *et al.* 1996), were demonstrated. Mostly accepted is the opinion that various categories of positive and negative cognitions have a relationship to the prefrontal cortex (Casey *et al.* 2004) and that prefrontal cortex, in turn modulates the subcortical fear response (Berkowitz *et al.* 2007) . In fMRI perspective, the brain response to emotional stimuli is significantly related to the task type during the fMRI examination (Lange *et al.* 2003).

In the treatment of PD, psychotherapy is widely used and CBT is often considered as an effective and promising next-step strategy for patients with panic disorder (Rodrigues *et al.* 2011). But we are still missing clear evidence that cognitive therapy, exposure therapy and CBT are more effective in PD treatment than other approaches (Norton & Price 2007; Otte 2011; Ougrin 2011; James *et al.* 2015). Despite the lack of such evidence, CBT is the most investigated psychotherapeutic approach in neuroimaging studies. As stated above, sufficient therapeutic response to CBT was associated with increased reactivity to threatening stimuli and retained ability to recognize safe stimuli. Moreover, conversely, less ability to distinguish between threat and safety, the persistence of increased emotional response to insignificant stimuli and slower extinction of fear conditioned response, are present in non-responders and patients

compared with controls. Increased prefrontal activation within the task, where the control over the emotional states is required, is associated with a good response to CBT (Reinecke *et al.* 2014). On the other hand, the passive emotional tasks have been repeatedly associated with increased prefrontal activation in non-responders to CBT and patients compared with controls (Maddock *et al.* 2003; Grambal *et al.* 2015). We suggest that excessive activation to passively received emotional stimuli may be the characteristic sign of the poorer response, possibly reflecting impaired cognitive control of emotions, a crucial skill required for successful CBT treatment.

If we focus on link between the prefrontal areas and subcortical fear networks, increased functional connectivity has been repeatedly found in PD patients when the fMRI task required top to bottom emotional regulation and was then associated with a good response to CBT (Kircher *et al.* 2013; Lueken *et al.* 2013, 2015). Functional connectivity reflects the strength of a bond between the brain regions, either positive or negative. It can describe only the temporal correlation between spatially remote neurophysiological events, but says nothing about the direction of action within these bonds. In terms of CBT model, both the negative (increases anxiety) and the positive (reduces anxiety) cognitions affect emotions (Casey *et al.* 2004).

Functional MRI cannot read the thoughts and increased regional brain activation can be associated with both positive and negative cognitions. Some authors suggest specific involvement of prefrontal areas in emotional regulation and control. Dorsal PFC function is proposed to be linked with appraisal and expression of fear (Milad & Rauch 2007) , whereas ventral PFC is linked with an inhibitory role of negative emotions. The strength of functional connectivity between prefrontal cortex and emotional brain structures, depending on the type of cognition, may be desirable or undesirable. Strengthening of negative emotions is associated with the amygdala – dorsal PFC connectivity and the amygdala – ventral PFC connection is linked with the control of negative emotions (Etkin *et al.* 2011). Changes at the local levels as well as mutual connectivity, we have to evaluate strictly in terms of task type, instructions received prior to the fMRI scanning and patient's feedback after the fMRI investigation.

Diagnosis of the panic disorder, as well as other psychiatric disorders, is based on the presence and absence of defined symptoms. However, symptoms say nothing about its neural substrate and endophenotype. We can simply imagine that a different type of imbalance within neuronal networks involved in panic disorder will lead to the same symptoms. From a current neurobiological perspective, we should see the panic disorder as an etiologically heterogeneous group disorder, which is manifesting by similar symptoms. Differences of endophenotype should be reflecting the unique personal history (destiny) of interactions between the dispositions and the environment.

At the cognitive level, the personal experiences are transformed into simplified personal beliefs, named as schemes (Beck 1988, 1991). Specific dysfunctional beliefs in panic disorder were described (Wenzel *et al.* 2006). After inclusion of the emotional level of the individual experiences by Jeffrey Young, schemas are more broadly understood as a complex self-defeating emotional and cognitive patterns established from childhood and repeated throughout life (Schmidt *et al.* 1995). We can say that a person experiences and responds to the world, whose image is strongly determined by their schemas. One of the recent studies, used 55 regions of the brain and their interactions during fear conditioning task, to predict individual therapeutic response and in 80% of cases the individual prediction was successful (Hahn *et al.* 2015). Such data increasingly indicate that the simplified models can be suitable for the study of general disorder regularities, but can hardly explain individual differences in response to therapy.

The effects of psychotherapy on brain function were repeatedly discussed. Through the diagnosis and psychotherapeutic interventions, there is no consensus on how the psychotherapy changes the brain functions. Hypothetically, neurobiological changes after psychotherapy can occur in regions that showed significant pre-treatment alteration. The other possibility is that psychotherapy acts through the recruitment of additional areas that did not show altered pre-treatment activation or a combination of the two (Roffman *et al.* 2005; Linden 2006; Abbass *et al.* 2014; Barsaglini *et al.* 2014; Beauregard 2014). Speculatively, when we try to integrate the neuroimaging and psychotherapeutic perspectives, the effect of CBT and the corresponding brain response could be expected primarily in prefrontal areas. Moreover, emotionally oriented therapeutic schools may instead influence the emotional brain network. However, most of the current therapeutic approaches combine both the cognitive work with exposure therapy and emotional work. In addition, we can confidently expect, that change in any part of the system, will be transferred to the other connected areas.

If we try to integrate all different models and findings of panic disorders, we can say that PD is a complex disorder with a heterogeneous symptoms manifestation and certainly with a different individual neurobiological substrate across the patients. Disturbance have been described in motor, behavioral, cognitive and emotional domains. We suggest that the combination of increase and/or decrease activity in many brain regions and strengthened or weakened connectivity between them can provide a neurobiological explanation for the wide variety of different symptoms and individual response to therapy. Individual vulnerability to the development of panic disorder may be understood as a consequence of the mutual interaction between the congenital factors, childhood formative influences, and other life events. Differences in fMRI (neuroimaging)

endophenotypes are influenced by highly individual personal history and should reflect the unique interactions between the dispositions and the environment (destiny). If 1 to 5 regional responses or characteristics can predict the patient "group" response to therapy, and 55 regions will predict individual response in 80% of patients, one can speculate that 100% prediction for an individual would require evaluating a very large number of brain areas, approaching infinity, which agrees with the philosophical perspective of the uniqueness of an individual. The difficulty of response prediction and the whole set of factors influencing an individual response to PD therapy support the view that guidelines cannot cover each individual and that clinical medicine – as far as it cares for an individual patient – will still remain an art (besides being a science).

LIMITATIONS OF CURRENT STUDIES

MRI methods are likely the most currently used tool in neuroscience research. Despite progress in functional MR imaging over the past 20 years, there are still technical limitations that arise from the method itself. Other limitations of fMRI result from inadequate consideration of the circuitry and functional organization of the brain, as well as from inappropriate experimental protocols that ignore this organization (Logothetis 2008). Further advances in fMRI research promise to push forward from mere cartography to the accurate study of brain organization. Functional MRI limitations in neuroscience research can be reduced by a multimodal approach, which is more necessary than ever for the study of the brain function and dysfunction. The combination of fMRI with other non-invasive techniques that directly assess the brain's electrical activity and a profound understanding of the neural basis of hemodynamic responses and animal invasive experimentation seem to be necessary (Logothetis 2008).

Many factors modify the response to specific stimuli employed in the fMRI examination. For interpreting the results, it is not only the type of stimulation, which is important, but in particular also the type of instruction provided before the functional MRI investigations. Instructions are known to modulate neural responses to emotional stimuli (Lange *et al.* 2003). More specifically, both the active (Reinecke *et al.* 2014) and passive (Grambal *et al.* 2015) emotional task could lead to stronger prefrontal activation, in a similar type of stimulation, where obviously the findings would suggest the opposite cause or explanation. Another particular factor influencing the fMRI signal is hypocapnia, which is frequently observed in panic patients hyperventilating during stressful procedures. fMRI examination by itself can lead to the stress response (Lueken *et al.* 2011). The brain BOLD responses of the panic patients in the scanner can be reduced by presence of anxiety (Maddock & Carter 1991; Posse *et al.* 1997) and simultaneously, increase of sensitivity to pH dysregulation is one of studied variables in panic disorder (Goossens *et al.* 2014; Magnotta *et al.* 2014).

In most of the above the mentioned studies, there is a number of general limitations related to the included patients. The common problem is still the small sample size, which places high demands on the homogeneity of the cohort. But it is difficult to reach the patients homogeneity while there is a poor knowledge of probably multifactorial influences affecting the individual endophenotype (Ball *et al.* 2014; Hahn *et al.* 2015) in patients with panic disorder. The lower number of probands may lead to the appearance of false positive differences, or vice versa can conceal truly present group differences (false negativity), even with otherwise sound methodology. Comorbid anxiety disorders, depression or personality disorders are usually present in panic patients. Despite the limitations resulting from the additional heterogeneity level, patients with comorbid disorders (including personal history) are more representative of the real patients in psychotherapeutic departments. On the other hand, it can be difficult to compare findings across the studies. For some types of emotional tasks, especially emotional face processing tasks, results may be strongly influenced by personality traits (Blair 2010; Mitchell *et al.* 2014). From the fMRI perspective, neutral emotional expressions probably cannot be considered as an activating neutral? (Donegan *et al.* 2003; Ohrmann *et al.* 2010). Despite that, some studies compared emotional faces with neutral ones as a control task (Ottaviani *et al.* 2012; Killgore *et al.* 2014). Another known variable that can influence the results is different gender proportions. Equal representation of men and women in the studies is associated with a risk of neutralization tied to sex effect (Ohrmann *et al.* 2010). Recently, several studies were also devoted to genetic influences on panic disorder (Domschke *et al.* 2006), (Domschke *et al.* 2008) and patient response to CBT (Straube *et al.* 2014).

In research on the effects of different psychotherapeutic approaches, it is difficult to avoid methodological inconsistency. Psychotherapy can influence the anxiety disorders specifically or nonspecifically (supportive strategies) and there is an ongoing discussion about the efficient therapeutic factors, across the therapists and therapeutic schools. Comparison of treatment response of panic patients to CBT confirmed that limited conclusions can be drawn about how to match anxiety disorder patients to specific treatment (Schneider *et al.* 2015). While some therapeutic schools and approaches are faced with methodological problems (Otte 2011; Wolitzky-Taylor *et al.* 2012; Markowitz *et al.* 2014), other ones are still waiting for definite proof of their effectiveness in treatment of anxiety disorders (Leichsenring 2005; Gibbons *et al.* 2008). While behavioral therapy, exposition-based CBT and CBT can be easily standardized, it is more difficult to perform standardization in other approaches, and often the therapists are not research-oriented.

FUTURE DIRECTIONS

There are many theoretical options to refine our understanding of the panic disorder. On the side of functional MR imaging, we can continue to optimize the scanner sequences and parameters, limit the presence of artifacts, improve the sensitivity and statistical processing. Another option is to use a combination of different MRI approaches such voxel-based morphometry (VBM), diffusion tensor imaging MR (DTI), MR spectroscopy (MRS) and resting-state MRI, to complement the common task-based functional MRI. The purpose of these functional methods is to understand better the local morphological and functional changes and the morphologic, functional, efficient and dynamic connectivity in panic disorder. Simultaneously with the previous options, it will be beneficial, to capture the electrophysiological parameters of the brain and other physiological and autonomic parameters that can reflect the patient's condition during the examination. Finally, in light of new techniques and deeper understanding of the panic disorder, re-analyzing former fMRI data can bring a different perspective, interpretations and findings.

To reduce the influence of anticipatory anxiety and anxiety during the examination, it is important to maximize consistent setting of environment before and during the functional MR examination. However, as mentioned, the most important factor for fMRI finding interpretation, is the standardization of the task themselves, clear and unambiguous instructions for the patients before the examination. More specifically, when the patients are exposed to their emotions during the examination, it is important whether they have to be passive or active when working with them. Furthermore, it is desirable to increase the amount of behavioral data, acquired both during fMRI examinations and outside of the scanner. It is important to obtain feedback for what the patients have emotionally experienced and how they have solved the task during the fMRI task.

For the patients, it is important to limit comorbid psychiatric disorders (including personality disorders) and medication in patients with panic disorder. Due to insufficient knowledge of parameters that shape the uniqueness of patient's endophenotype, increasing number of patients and controls may not bring the further progress in understanding to the individual patient. Specific inter-individual differences can easily skew group analyses, unless some outlier correction is attempted. There is a requirement for more specific investigative tests, focusing on the differences in the expression of panic disorder, genetic predisposition, children's formative influences and life events, current life context and revealing individual cognitive-emotional style (schemas).

When examining the psychotherapy effectiveness, there is a strong need to improve the methodological consistency and rigor of treatment moderator studies. With the advances in understanding the active factors of therapy, in combination with the biomarkers, it could be possible to personalize the treatment focusing on the individual needs of patients.

The betters we can fulfill the above conditions, the more likely it seems that we will move from understanding the disorder to understanding the patient. We can recommend a combination of two approaches to make such progress. According to current knowledge, we should aim to reduce the inhomogeneity in the sample of patients, standardize the tasks and the fMRI examination on one hand and to maximize the recording of potential modifying factors on the side of patients.

CONCLUSION

The current findings are broadly in accordance with the revised Gorman's model of panic disorder on group analysis. For the reasons described, the results of individual studies are often inconsistent, and it is difficult to compare them. It is necessary to take into account all possible modifying factors when evaluating the fMRI findings in panic disorder. Considering the current neuroscientific evidence, the appealing clinical concept of panic disorder as a homogeneous unit is increasingly dissolving. Mapping highly individual factors of patient's history and interaction of biological factors with the environment are the challenges for the future research. Whereas brain imaging has brought a significant progress in the past decades, the psychological factors are still insufficiently explored. Further development will be necessary at all research levels for the integration of different biological, psychological and social factors. Further progress may result in better understanding of individual factors which modify the panic disorder symptoms and treatment response and may lead to increased ability to treat the patient, not the diagnosis. In our opinion, there is a growing evidence that the uniqueness of human destiny is specifically inscribed in the almost infinitely variable human brain neural networks and influences the observed variability of symptoms, not only in panic disorder. We assume that the original view of panic disorder as a well-demarcated disorder will be gradually abandoned and that neuroscientists and the psychotherapists will be in agreement. In light of new findings and insights, it seems appropriate to put an excessive optimism to rest, avoid premature conclusions and maintain the humility for future research adventures.

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