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The neural correlates of cognitive behavioral therapy: Recent progress in the investigation of patients with panic disorder

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ABSTRACT

Cognitive behavioral therapy (CBT) is an evidence-based treatment for mental disorders. Several meta-analytical reviews supported its efficacy and effectiveness in the treatment of panic disorder with agoraphobia (PD/AG). Recently, it has been shown that neurobiological changes are associated with the process and outcome of CBT. However, the general and specific neurobiological effects of CBT are still widely unknown. Therefore, the potential of applying neuroscience to clinical practice and optimizing CBT is still limited. The current review summarizes recent findings about the neural correlates of CBT in PD/AG measured with fMRI. Furthermore, the current review will focus on neural activation patterns predicting and moderating therapeutic success of CBT, due to its potential application in personalized treatment in the future. Finally, we will discuss some future perspectives of the neurosciences in CBT research.

Introduction

After more than 50 years of development and research on cognitive behavior therapy (CBT), this treatment has become the most widely used and effective evidence-based treatment for many mental disorders (Beck & Dozois, 2011). Meta-analyses of efficacy and effectiveness support its therapeutic effect across a wide range of symptoms and treatment settings (Butler, Chapman, Forman, & Beck, 2006; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Stewart & Chambless, 2009). With the introduction of neuroimaging techniques, such as positron emission tomography (PET), structural and functional magnetic resonance imaging (sMRI/fMRI), and single photon emission tomography (SPECT) in psychotherapy research (Carrig, Kolden, & Strauman, 2009; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; Weingarten & Strauman, 2014), the neurobiological correlates of therapeutic change in CBT have been increasingly investigated. A number of more recently published reviews on the neuroscience of psychotherapy suggest that *neurobiological changes are associated with the progress and outcome of psychotherapy.* The majority of the reviewed research is on the neural correlates of CBT (e.g., Barsaglini, Sartori, Benetti, Pettersson-Yeo, & Mechelli, 2014; Messina, Sambin, Palmieri, & Viviani, 2013; Thomaes et al., 2014; Weingarten & Strauman, 2014). However, previous neuroimaging studies about CBT effects have only proved the concept which shows that changes of the mind through CBT and changes in the brain are somehow intercorrelated (e.g., Prasko et al., 2004; Sakai et al., 2006). The neurobiological mediator and moderator of CBT effects are widely unknown, which makes it very difficult to apply these findings to clinical practice. An in-depth neuroimaging study of CBT needs to reveal the mechanism of action in CBT (Gloster et al., 2009). Neuroscientific information could provide a new foundation for the optimization and individualization of CBT treatments. However, sophisticated and well-controlled neuroscientific experimental designs embedded in randomized controlled trials (RCTs) are needed for the advancement of this endeavor (Kraemer, Wilson, Fairburn, & Agras, 2002).

Until now, the modulation of brain physiology with CBT in panic disorder (PD) has been investigated only in two PET studies (Prasko et al., 2004; Sakai et al., 2006), one SPECT study (Seo, Choi, Chung, Rho, & Chae, 2014) and two fMRI studies (Kircher et al., 2013; Straube et al., 2014). The two PET studies and the one SPECT study used a resting state paradigm, in which the patients solely had to rest in the scanner. Resting state activity does not provide specific brain states in subjects. Therefore, the direct association of the change in neural activation during resting state and the change in behavior is hard to draw. Although the two PET and one SPECT studies provide first support for CBT modulating brain activation in

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PD, their results may not be regarded as fully conclusive since the three studies included only a small number of patients (6 patients, 11 patients, and 14 patients). Ball, Stein, Ramsawh, Campbell-Sills, and Paulus (2014) used pretreatment fMRI data during an emotion regulation task to predict CBT response of patients with PD and generalized anxiety disorder. However, combination of two diagnostic groups enlarged the heterogeneity of patients. Above all, none of the four studies investigated the mediators and moderators of CBT. Here we summarize findings of a set of related fMRI studies about the neural correlates of CBT in PD (Kircher et al., 2013; Lueken et al., 2013; Reif et al., 2014; Straube et al., 2014), which are based on a large-scale multicenter study named "PANIC-NET". This multicenter study is characterized by its theoretical foundation rooted in classical fear conditioning, the implementation of a large-scale RCT, the comparison of two variants of manualized CBT and the investigation of moderators of CBT.

From 2006 to 2013, the German Federal Ministry of Education and Research (BMBF) funded this project on the investigation of CBT on PD/AG with large scale RCTs. This "PANIC-NET" multicenter research project was aimed to optimize CBT and to understand its mechanisms of action (Gloster et al., 2009). Three hundred sixty-nine medication-free patients were recruited nationwide in Germany and treated with two variations of CBT, which are distinguished by therapist-guided and self-guided exposure (Gloster et al., 2011). Experimental add-on studies on fear circuit mechanisms in PD/AG using psychophysiological tests and fMRI were also conducted before and after the treatments, as well as genotyping. More detailed information about the subjects, methodology and fMRI quality assurance is obtainable in the Appendix and the original publications (Gloster et al., 2011; Kircher et al., 2013; Lueken et al., 2011; Lueken et al., 2014; Straube et al., 2014).

Our review will focus on an experimental fear conditioning paradigm, which was administered two times, eight weeks apart, during fMRI data acquisition in patients with PD/AG and healthy control subjects. First, we investigated general differences of brain activation between patients before treatment and healthy subjects (Lueken et al., 2014). Second, we revealed the neural activation changes due to both types of CBT treatment (Kircher et al., 2013). Furthermore, the two CBT types (therapist-guided versus self-guided exposure) were compared to reveal the therapeutic contribution of particular CBT component (Straube et al., 2014). The large number of patients made it possible to compare therapy responders and non-responders in their neural activations at baseline (Lueken et al., 2013), as well as to predict the therapy outcome at the individual basis using machine learning algorithms (Hahn et al., in press). Moreover, the neural correlates of moderator effects of genotype in CBT were examined (Reif et al., 2014). Together, the investigations give an overview of possible study designs (see Table 1) and how these can contribute to the understanding of the mechanisms of action in CBT and in the long run to personalized therapy (see Fig. 1). The current review will end with a discussion about the future perspectives of neuroscience in CBT research.

Fear conditioning in healthy subjects

Fear conditioning has been proposed to represent a core pathway for the development and maintenance of PD/AG (Bouton, Mineka, & Barlow, 2001). Current studies suggest enhanced simple conditioning (Lissek et al., 2005), deficient safety signal processing as indicated by enhanced responses towards a safety cue (Lissek et al., 2009), or increased resistance to extinction learning, demonstrating a more persistent recall of the conditioned response (Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007) as the underlying learning deficit of PD/AG. The neural network of fear conditioning has been extensively studied in healthy subjects using fMRI (for a review see Sehlmeyer et al., 2009). Extending animal research, which usually is focused on the amygdala as a key region (Ledoux, Iwata, Cicchetti, & Reis, 1988), fMRI studies revealed a cortical and subcortical network encompassing the thalamus, amygdala, hippocampus, insula, anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) to be involved in human fear conditioning (Sehlmeyer et al., 2009). This network has a substantial overlap with fear circuitry structures that show abnormal activation in different anxiety disorders (Etkin & Wager, 2007; Shin & Liberzon, 2010), further supporting the suitability of fear conditioning as a behavioral probe to investigate the neural substrates of anxiety disorders (Gorman, Kent, Sullivan, & Coplan, 2000).

To elucidate neural substrates of fear conditioning in PD/AG patients and their changes by CBT, a differential fear-conditioning task was developed for the "PANIC-NET" multicenter study (Reinhardt et al., 2010). The task consisted of three phases: familiarization, acquisition, and extinction (for illustration see Fig. 1). During fear acquisition, one neutral stimulus (CS+) was paired with an aversive auditory tone (US), whereas, the other neutral stimulus (CS−) was presented alone. A partial reinforcement rate of 50% was employed. Neural correlates of differential conditioning (CS+ vs. CS− during acquisition), simple conditioning (CS+ during acquisition vs. CS+ during familiarization) and safety signal processing (CS− during acquisition and extinction vs. CS− during familiarization) could be investigated by this task.

Demonstrated by a pilot study with 20 healthy subjects, the differential fear-conditioning task showed its applicability for the evaluation of neural correlates of fear conditioning and extinction (Reinhardt et al., 2010). The differential conditioning was associated with increased activation in the fear circuit, such as amygdala, insulae, ACC and parahippocampal gyrus, for CS+ in contrast to CS−. These activations are in line with the previous studies on classical aversive conditioning (for a review see Sehlmeyer et al., 2009). Additionally, a linearly decreasing activation in the right amygdala/hippocampus for the CS− across the acquisition phase was found (Reinhardt et al., 2010). Thus, the differential fear-conditioning task is a promising paradigm for the examination of the fear-circuit in patients with anxiety disorders, including PD.

Fear conditioning in PD/AG

Among the enrolled 369 medication-free patients with PD/AG in the "PANIC-NET" multicenter study, 89 patients performed the aforementioned differential fear-conditioning task during fMRI measurement at baseline (Kircher et al., 2013). After a quality control process, fMRI data from 60 patients were compared with 60 matched healthy controls to reveal the altered neural processing of fear conditioning in PD/AG (Lueken et al., 2014). This fMRI subsample of patients revealed the same level of symptom severity as the entire sample of 369 patients (see Appendix and Lueken et al., 2014). However, the fMRI results could still be limited in their generalizability to a broader clinical population because of potential selection bias due to the fMRI procedure (e.g., exclusion criteria for MRI scan).

This comparison yielded the following key results: (1) PD/AG patients showed enhanced midbrain periaqueductal gray (PAG) activity during simple conditioning and safety signal processing compared to healthy subjects (see Fig. 1, Lueken et al., 2014). While the midbrain PAG is an integral part of the brain system mediating defensive reactivity under threat (Brandao, Zanoveli, Ruiz-Martinez, Oliveira, & Landeira-Fernandez, 2008), this activation was interpreted in terms of bottom−up (basic defensive system) processing during fear conditioning in PD/AG (Lueken et al., 2014). When confronted with the potential presence of an aversive stimulus (US), patients appeared to activate defensive system

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