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Research report

Separating depressive comorbidity from panic disorder: A combined functional magnetic resonance imaging and machine learning approach

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ABSTRACT

Background: Depression is frequent in panic disorder (PD); yet, little is known about its influence on the neural substrates of PD. Difficulties in fear inhibition during safety signal processing have been reported as a pathophysiological feature of PD that is attenuated by depression. We investigated the impact of comorbid depression in PD with agoraphobia (AG) on the neural correlates of fear conditioning and the potential of machine learning to predict comorbidity status on the individual patient level based on neural characteristics.

Methods: Fifty-nine PD/AG patients including 26 (44%) with a comorbid depressive disorder (PD/AG+DEP) underwent functional magnetic resonance imaging (fMRI). Comorbidity status was predicted using a random undersampling tree ensemble in a leave-one-out cross-validation framework.

Results: PD/AG−DEP patients showed altered neural activation during safety signal processing, while +DEP patients exhibited generally decreased dorsolateral prefrontal and insular activation. Comorbidity status was correctly predicted in 79% of patients (sensitivity: 73%; specificity: 85%) based on brain activation during fear conditioning (corrected for potential confounders: accuracy: 73%; sensitivity: 77%; specificity: 70%).

Limitations: No primary depressed patients were available; only medication-free patients were included. Major depression and dysthymia were collapsed (power considerations).

Conclusions: Neurofunctional activation during safety signal processing differed between patients with or without comorbid depression, a finding which may explain heterogeneous results across previous studies. These findings demonstrate the relevance of comorbidity when investigating neurofunctional substrates of anxiety disorders. Predicting individual comorbidity status may translate neurofunctional data into clinically relevant information which might aid in planning individualized treatment. The study was registered with the ISRCTN: ISRCTN80046034.

1. Introduction

Depression is the most frequent comorbid condition in panic disorder with agoraphobia (PD/AG), affecting nearly every second patient (Emmrich et al., 2012; Goodwin et al., 2005; Kessler et al., 2006; Roy-Byrne et al., 2000). Comorbid depression is associated with more severe panic symptomatology (Emmrich et al., 2012; Roy-Byrne et al., 2000) and overall impairment (Roy-Byrne et al.,

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2000). Yet, our knowledge about shared and distinct pathophysiological mechanisms in PD/AG patients with or without comorbid depression is limited; research on the neural substrates of PD/AG may be biased if comorbid depression is present. Beyond this phenotype perspective on the group level, there is a critical need to translate neuroimaging findings into clinically useful information for the individual patient. Multivariate pattern recognition employing machine learning generates predictive information that can be used for single subject classification, thus offering new tools to translate neuroimaging findings into diagnostic value for the individual patient (Orru et al., 2012). Hence, we complemented our conventional group analysis on the effects of depressive comorbidity on the neural substrates of fear conditioning by predicting depressive comorbidity status for the individual patient within a machine-learning framework.

Fear conditioning is a basic learning process with fundamental relevance for the survival of an organism. During differential fear conditioning, contingencies are established by pairing an aversive unconditioned stimulus (US) with a previously neutral stimulus (conditioned stimulus; CS+). While the CS+ signals are the potential presence of a threat, a second neutral stimulus (CS−) that is never paired with the US becomes a signal for safety. The neural network of fear conditioning has been extensively studied in humans using functional magnetic resonance imaging (fMRI). Extending animal research focusing on the amygdala as a key region (LeDoux et al., 1988), further cortical and subcortical networks encompassing the thalamus, amygdala, hippocampus, insula, anterior cingulate cortex (ACC) and prefrontal/orbitofrontal cortex (PFC/OFC) have been shown to be activated during human fear conditioning (Sehlmeyer et al., 2009). Of note, this "threat network" has substantial overlap with structures that show abnormal activation in different anxiety disorders (Etkin and Wager, 2007).

Fear conditioning represents a central pathway for the development and maintenance of PD/AG (Bouton et al., 2001; Dresler et al., 2012; Kircher et al., 2013; Lueken et al., 2014), but the precise nature of fear learning deficits still remains under debate. Behavioral studies showed that PD may be characterized by excessive fear responding toward the safety signal (CS−) when compared to the threat signal (CS+) (Lissek et al., 2009). In line, using an instructed fear conditioning paradigm Tuescher et al. (2011) demonstrated increased neural activation in threat network structures such as the subgenual cingulate, ventral striatum and extended amygdala, as well as in the midbrain periaqueductal gray during the processing of safety cues compared to the threat condition. This response pattern was specific for PD when compared to posttraumatic stress disorder (PTSD) patients. However, the influence of comorbid depression on the reported brain activation pattern remains unresolved, since comorbid patients were not excluded and subgroup analyses were not feasible in this sample of eight patients. In a similar vein, we (Lueken et al., 2013) recently reported increased activation in a network related to threat (anterior cingulate cortex, hippocampus, and amygdala) during fear conditioning in response to the safety signal (CS−) compared to the threat signal (CS+) as a pre-treatment feature of non-response to CBT in a sample of medication-free PD/AG patients. However, depression comorbidity was allowed unless being clinically the primary diagnosis (Gloster et al., 2011).

While increased responding to stimuli that signal safety may underlie the onset and maintenance of anxiety disorders (Duits et al., 2015), recent evidence suggests that this pathomechanism is moderated by the presence of comorbid depression. The magnitude of fear reactions under safe conditions is a specific risk factor for the development of anxiety, but not depressive disorders (Craske et al., 2012). Specifically, startle potentiation under different threat conditions was diminished in PD when comorbid depression was present (Melzig et al., 2007). Similar findings on impaired fear inhibition toward safety signals as a feature of anxiety, but not depression have been reported in PTSD (Jovanovic et al., 2010). The influence of comorbid depression on the neural correlates of safety signal processing in PD/AG remains still unresolved as previous studies did not consistently report or control for comorbid depression, which can be mainly subjected to power restrictions in small-scale studies.

The aim of the present study therefore was twofold: using a comprehensive sample of 59PD/AG patients with a substantial proportion exhibiting a comorbid depressive disorder, we investigated whether the neural correlates of safety signal processing differed between PD/AG patients with and without comorbid depressive disorders (PD/AG+DEP; PD/AG-DEP). Second, translating these findings into clinically useful information, we tested the potential of machine learning to predict depressive comorbiditiy on an individual patient level based on neural characteristics. Following previous evidence from behavioral investigations (Craske et al., 2012; Duits et al., 2015; Melzig et al., 2007) we hypothesized that altered safety signal processing in brain areas subserving the detection of threat (e.g. amygdala, anterior cingulate cortex, and insula) should be most pronounced in patients without comorbid depression. Dimensional markers of panic symptomatology, but not depression, were expected to correlate with the magnitude of neurofunctional activation patterns during safety signal processing.

2. Methods

2.1. Subjects

As a part of the German research network "PANIC-NET", including a randomized controlled clinical trial on exposure-based CBT in PD/AG (Gloster et al., 2011), current results represent a secondary analysis supplementing the main fMRI publication (12). Eight German centers participated in the clinical trial (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, Würzburg) treating 369 patients who met DSM-IV-TR criteria for PD/AG. At four centers (Aachen, Berlin-Charité, Dresden, Münster) an fMRI add-on study was conducted. From 369 patients enrolled in the clinical trial, 194 were recruited at fMRI centers, and of these 89 patients consented to participate in the present study. 60 Quality controlled baseline data sets were available. Details on the study protocol (including a CONSORT flowchart), in- and exclusion criteria and measures of fMRI data quality control are given elsewhere (Gloster et al., 2011; Kircher et al., 2013). One patient without complete diagnostic information on comorbidity patterns had to be excluded, leaving $n=59$ patients for the present analysis. Briefly, currently only (i.e. 4-week washout period) medication-free patients with a primary diagnosis of PD/AG according to DSM-IV-TR criteria as assessed by a standardized interview (Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIAX-CIDI version; Wittchen and Pfister, 1997)) which was validated by clinical experts, a Hamilton Anxiety Scale Score (SIGH-A; Shear et al., 2001) ≥ 18, a Clinical Global Impressions Score (CGI; Guy, 1976) ≥ 4 and aged 18–65 years were included. Inability to comply with the study schedule, clinically significant suicidal intent, diagnostic criteria for any psychotic or bipolar disorder, borderline personality disorder, or current alcohol dependence, medical conditions explaining anxiety symptoms and MRI-related contraindications were followed by exclusion. Current comorbid diagnoses, including major depression, dysthymia and other anxiety disorders were allowed unless they were of primary clinical concern. As such, this sample can be considered both relatively severe and representative of patients