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Research paper

Sample heterogeneity in unipolar depression as assessed by functional connectivity analyses is dominated by general disease effects

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ABSTRACT

Objectives: Combinations of resting-state fMRI and machine-learning techniques are increasingly employed to develop diagnostic models for mental disorders. However, little is known about the neurobiological heterogeneity of depression and diagnostic machine learning has mainly been tested in homogeneous samples. Our main objective was to explore the inherent structure of a diverse unipolar depression sample. The secondary objective was to assess, if such information can improve diagnostic classification.

Materials and methods: We analyzed data from 360 patients with unipolar depression and 360 non-depressed population controls, who were subdivided into two independent subsets. Cluster analyses (unsupervised learning) of functional connectivity were used to generate hypotheses about potential patient subgroups from the first subset. The relationship of clusters with demographical and clinical measures was assessed. Subsequently, diagnostic classifiers (supervised learning), which incorporated information about these putative depression subgroups, were trained.

Results: Exploratory cluster analyses revealed two weakly separable subgroups of depressed patients. These subgroups differed in the average duration of depression and in the proportion of patients with concurrently severe depression and anxiety symptoms. The diagnostic classification models performed at chance level.

Limitations: It remains unresolved, if subgroups represent distinct biological subtypes, variability of continuous clinical variables or in part an overfitting of sparsely structured data.

Conclusions: Functional connectivity in unipolar depression is associated with general disease effects. Cluster analyses provide hypotheses about potential depression subtypes. Diagnostic models did not benefit from this additional information regarding heterogeneity.

1. Introduction

Patients with major depressive disorder (MDD) present with a variety of symptoms (American Psychiatric Association, 2013; World Health Organization, 2004). There is a longstanding debate about possible subtypes in MDD, which focused on the clinical heterogeneity in symptomatology and course of the disease (Fried and Nesse, 2014; Harald and Gordon, 2012; Ten Have et al., 2016). Recently, a complementary perspective on heterogeneity of MDD has emerged: It has been hypothesized that MDD may actually be a group of biologically distinct disorders with a clinically non-distinguishable presentation (Krishnan, 2014). This idea is in line with the more general observation that neuroscientific findings do often not map well onto categorical clinical diagnoses in psychiatry. This experience has been a main motivation for the research domain criteria (RDoC) initiative of the American National Institute of Mental Health (NIMH). The RDoC initiative promotes the development of dimensional constructs of mental diseases, thereby integrating elements of psychology and neuroscience as an alternative to conventional diagnostic categories (Kozak and Cuthbert, 2016). Despite an extensive amount of research on neurobiological mechanisms in MDD (Kupfer et al., 2012), efforts to develop reliable biomarkers for the current categorical disease concept in individual patients generally lag behind expectations (Kambeitz et al., 2016; Phillips et al., 2015; Schneider and Prvulovic, 2013; Sundermann et al., 2017).

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Functional magnetic resonance imaging (fMRI), in particular resting-state fMRI (rs-fMRI) has been hypothesized to be an important constituent of defining an intermediate endophenotype of depression, thereby filling a gap in the pathway from genetic variation to the distal, clinically apparent disorder (Hasler and Northoff, 2011). Spontaneous signal fluctuations at rest measured by rs-fMRI are deemed to represent functional connectivity (FC) and thus neural interactions of multiple brain regions (Barkhof et al., 2014; Friston et al., 1993; van den Heuvel and Hulshoff Pol, 2010). Rs-fMRI has been frequently used to study group effects in depression and has mainly pointed towards alterations of brain networks related to self-referential processing and executive control as well as their interactions (Kaiser et al., 2015; Mulders et al., 2015; Sundermann et al., 2014b). In recent years there have been substantial efforts to utilize such findings to develop diagnostic biomarkers by combining fMRI and multivariate pattern analysis (MVPA) techniques. Despite promising results in pilot studies in depression (Bhaumik et al., 2016; Cao et al., 2014; Craddock et al., 2009; Guo et al., 2014; Lord et al., 2012; Ma et al., 2013; Qin et al., 2015; Yu et al., 2013; Zeng et al., 2012, 2014a; Zhong et al., 2017) this concept has not yet been successfully translated into a reliable tool for real patient care (Arbabshirani et al., 2017; Haller et al., 2014; Kambeitz et al., 2016; Klöppel et al., 2012; Orru et al., 2012; Patel et al., 2016; Ramasubbu et al., 2016; Sundermann et al., 2014a; Wolfers et al., 2015; Woo et al., 2017), particularly in a clinically more realistic heterogeneous depression cohort (Sundermann et al., 2017).

Cluster analyses (CAs), a specific group of unsupervised machine-learning methods, facilitate the exploration of the inherent structure of datasets (James et al., 2013) such as large groups of patients. CAs can be utilized to generate hypotheses about potential subgroups. Hierarchical CA methods group individual measurements without assumptions on the number of subgroups and are therefore preferred in situations characterized by limited prior knowledge (James et al., 2013). Other CA techniques build upon prior assumptions. An example for the latter is the predefined number of subgroups for K-means clustering (Jain, 2010; James et al., 2013). Combining both methods alleviates dependence on such specific assumptions (James et al., 2013). A recent study has used a combination of unsupervised machine-learning techniques to jointly analyze functional connectivity and symptom profiles in treatment-resistant depression. The results suggested that patients might be subdivided into four putative “biotypes”. These findings were incorporated in successful diagnostic models (Drysdale et al., 2017). It remains unclear, if diverse depression samples can be subdivided into distinct groups based on neurobiological findings alone.

Aims of the study: The primary objective was to analyze the inherent structure of a large fMRI dataset from a diverse sample of patients with unipolar depression acquired during wakeful rest. Our intention was to generate hypotheses about potential biological subgroups defined by functional connectivity between brain regions which are known to be altered in depression at the group level. Based on these results we intended to test if such information helps to improve diagnostic MVPA-models.

2. Materials and methods

2.1. Subjects, data acquisition and feature extraction

The analyses performed to explore sample heterogeneity were based on resting state fMRI as well as clinical data from patients with unipolar depression from the BiDirect cohort (Hermesdorf et al., 2016; Rahe et al., 2015; Sundermann et al., 2017; Teismann et al., 2014; Teuber et al., 2017; Wersching and Berger, 2012). Additionally, derived diagnostic models were tested in a nested case-control design of patients with depression matched to community-dwelling controls, both within the BiDirect Study. The study was approved by the ethics committee of the University of Münster and the Westphalian Chamber of Physicians in Münster. Written informed consent for participation in the study was obtained from all participants. Patients with an episode of depression were recruited at psychiatric and psychosomatic hospitals and departments, as well as two resident private psychiatrists' practices (limited to patients who had been hospitalized due to depression at least once during the 12 months period prior to inclusion into the study). Inclusion criteria were (i) age (≥ 35 and < 66 years) and (ii) current in- or outpatient treatment due to acute depression. Exclusion criteria were (i) compulsory admission, (ii) comorbid dementia, and (iii) comorbid drug abuse. Potential participants were ascertained by trained and certified psychologists. Subjects for a reference cohort had been randomly sampled via population register and were invited via letter (Teismann et al., 2014). We applied additional selection and matching criteria in order to avoid potential biases (see below). Data acquisition involved clinical, psychological and neuropsychometric testing, and structural and functional MRI. Psychological assessment included the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), Hamilton Rating Scale for Depression (HAM-D-17) (Hamilton, 1960), Hamilton Rating Scale for Anxiety (HAM-A-14) (Hamilton, 1959) and parts of the Mini International Neuropsychiatric Interview (MINI) (Ackenheil et al., 1999).

1378 technically complete rs-fMRI datasets were obtained (see the Supplementary methods for details on MRI data acquisition). In each subject within this sample we conducted a standard correlation-based analysis of functional connectivity (FC) between pairs of regions of interests (ROIs). The selection of 38 ROIs for the main analyses was based on a meta-analysis (Sundermann et al., 2014b) and reflects regions which are known to exhibit altered FC or spontaneous local activity in unipolar depression. FC-analyses resulted in 703 unique features (z-transformed correlation coefficients) which were then used for CA and finally for diagnostic modelling. Additionally we extracted analogous FC features based on a parcellation of the whole brain into 200 ROIs (Craddock et al., 2012). See the Supplementary methods for a detailed description of FC analyses.

We selected matched subsamples of patients with unipolar depression and non-depressed controls from the entire sample. Details are provided in the Supplementary methods and were identical with our previous work (Sundermann et al., 2017). These samples were then randomly split in half. The resulting fully independent subsets used in the following analyses will be referred to as S1 and S2 throughout this article (see below for the detailed nomenclature of subsets and analyses). Each subset (S1, S2) comprised 360 study participants (unipolar depression: n = 180, controls: n = 180). Demographical and clinical characteristics of participants in S1 and S2 are shown in Table 1. Patients and control participants within S1 did not differ significantly regarding demographical characteristics.

The following nomenclature will be used to code subsets as well as cluster analyses and their results throughout this article (details on each step of the cluster analyses are provided in the following parts of the methods section):

1. Subset (S1: subset 1, S2: subset 2)
2. Cohort (D: unipolar depression, C: population controls)
3. Step of cluster optimization procedure (full: first step, symp: second step after exclusion of patients diagnosed with MDD but not currently symptomatic at the time of data acquisition)
4. Type of cluster analysis (HC: hierarchical, KM: K-means)
5. Cluster number within a particular cluster analysis (C1: cluster 1, C2: cluster 2 etc.)

Thus for example “S1Dsymp_KMC1” represents the first cluster resulting from a K-means cluster analysis within the group of currently symptomatic patients with unipolar depression from subset 1.

2.2. Multivariate data analysis

In the main analysis we conducted exploratory cluster analyses