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Predicting the Naturalistic Course of Major Depressive Disorder Using Clinical and Multimodal Neuroimaging Information: A Multivariate Pattern Recognition Study

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ABSTRACT

BACKGROUND: A chronic course of major depressive disorder (MDD) is associated with profound alterations in brain volumes and emotional and cognitive processing. However, no neurobiological markers have been identified that prospectively predict MDD course trajectories. This study evaluated the prognostic value of different neuroimaging modalities, clinical characteristics, and their combination to classify MDD course trajectories.

METHODS: One hundred eighteen MDD patients underwent structural and functional magnetic resonance imaging (MRI) (emotional facial expressions and executive functioning) and were clinically followed-up at 2 years. Three MDD trajectories (chronic $n = 23$, gradual improving $n = 36$, and fast remission $n = 59$) were identified based on Life Chart Interview measuring the presence of symptoms each month. Gaussian process classifiers were employed to evaluate prognostic value of neuroimaging data and clinical characteristics (including baseline severity, duration, and comorbidity).

RESULTS: Chronic patients could be discriminated from patients with more favorable trajectories from neural responses to various emotional faces (up to 73% accuracy) but not from structural MRI and functional MRI related to executive functioning. Chronic patients could also be discriminated from remitted patients based on clinical characteristics (accuracy 69%) but not when age differences between the groups were taken into account. Combining different task contrasts or data sources increased prediction accuracies in some but not all cases.

CONCLUSIONS: Our findings provide evidence that the prediction of naturalistic course of depression over 2 years is improved by considering neuroimaging data especially derived from neural responses to emotional facial expressions. Neural responses to emotional salient faces more accurately predicted outcome than clinical data.

Keywords: Clinical information, Course trajectory, Magnetic resonance imaging, Major depressive disorder, Prediction, Probabilistic pattern recognition analysis

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Major depressive disorder (MDD) is worldwide among the leading causes of disability (1) due to high prevalence, negative impact on quality of life, and its frequently recurrent or chronic character. Of all MDD patients, 20% to 25% are at risk for chronic MDD (2). Identifying predictors of chronicity at an early stage is of critical importance, because it can help to select treatment strategies specifically aimed at reducing factors associated with worse long-term clinical outcome.

In MDD, several clinical characteristics have been linked to a chronic course, including greater symptom severity, longer duration of an episode, number of episodes, comorbidity, earlier onset, childhood adversity, higher neuroticism, lower extraversion, and lower conscientiousness (2–7). However, these factors do not directly relate to underlying pathophysiological mechanisms and cannot fully capture interindividual differences in the course of MDD. It is essential to identify additional pathophysiological markers to guide treatment selection and eventually develop alternative treatment strategies. Neuroimaging might provide such biomarkers. On a structural level, reduced hippocampus and anterior cingulate cortex (ACC) volume may represent a vulnerability factor for poor outcome (8,9). On a functional level, aberrant activation related to emotional and cognitive processing (including executive functions) has been implicated (10). For example, alterations in activation in medial prefrontal regions including the ACC during processing of emotional stimuli predict relapse after 18 months in remitted MDD patients (11) and treatment response (12). In addition, abnormal dorsolateral prefrontal cortex (PFC) recruitment during visuospatial planning is related to a nonfavorable naturalistic course of MDD (Woudstra S, *et al.*, unpublished data, 2014). These neuroimaging findings, however, are based on group comparisons with unknown translational value. To make these results clinically useful, it is necessary to provide valid predictions at the level of the individual patient.

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Multivariate pattern recognition (MPR) methods have been applied to neuroimaging data to classify individuals as MDD patients or control subjects (13–19). MPR is a technique that allows classification of individuals into distinct classes based on high-dimensional data and is more sensitive for detecting spatially distributed effects, compared with univariate approaches, which aim to detect functionally localized differences.

These diagnostic MPR studies are an important first step, but the real potential of MPR is for predicting future outcome, such as treatment response or course trajectory. To date, only a few preliminary MPR studies have examined whether outcome can be predicted, showing accuracies of 65% to 89% (17,20–22). These studies all focused on small clinical samples of MDD patients recruited in specialized mental health care. Therefore, they capture patients with the most severe and recurrent MDD, who are more likely to be referred to specialized mental health care (23) and who represent only a small proportion of the spectrum of MDD patients. Because most MDD patients reside in the community and primary care, the generalizability of these MPR findings to a general population remains unclear. It is of great clinical relevance to predict the course of MDD in a sample derived from a more naturalistic setting where patients have a broad range of illness severity. Moreover, MPR studies to date have mostly focused on a single imaging modality. It is unknown which imaging modality or functional task provides the most accurate predictions of outcome. Finally, little is known about the added value of neuroimaging to predict MDD disease course relative to cheaper and more easily acquired measures such as clinical assessments.

The current aim was to employ MPR to identify predictors for chronicity of MDD. For this purpose, we employed Gaussian process classifiers (GPCs) to examine the potential of various imaging modalities including structural magnetic resonance imaging (MRI) and brain activity during emotional and cognitive processing. In addition to these imaging modalities known important clinical variables, such as baseline severity, duration, and comorbidity indicators and information on personality traits and childhood trauma, were used to discriminate between different MDD course trajectories in 118 individual patients with a current MDD diagnosis from a naturalistic cohort encompassing the broad heterogeneity of MDD.

METHODS AND MATERIALS

Subjects

After approval of the NEtherlands Study of Depression and Anxiety (NESDA)-MRI study by the ethical review boards of the three participating centers and written informed consent of participants, a subgroup (total $n = 301$; subjects with MDD diagnosis $n = 156$) of participants from the total NESDA study was included for MRI. Of these, for the current study, we included all 118 patients (82 female patients; aged 18–56) who had 1) baseline current (6-month) DSM-IV diagnosis of MDD, established using the structured Composite International Diagnostic Interview (24) and reporting symptoms in the month before baseline confirmed with either the Composite International Diagnostic Interview or the Life Chart Interview (LCI) (25); and 2) availability of 2-year follow-up of depressive symptoms measured with the LCI.

Definition of Two-Year Course Trajectory Groups

Based on a latent class growth analysis (LCGA) of follow-up data derived from the LCI [which was the source containing most detailed information on 2-year MDD course, previously conducted in a larger, overlapping sample (7)], MDD patients were divided in different course trajectories. Briefly, LCGA analysis, based on the burden of depressive LCI symptoms indicated for each of the 24 months between baseline and follow-up (with the first score representing the burden of symptoms in the month after baseline) was conducted in 804 MDD patients. The LCGA analysis identified five different classes of course trajectories: 1) a rapid remission trajectory; 2) a trajectory showing a gradual improvement of symptoms; 3) a second trajectory showing a gradual improvement of symptoms but with higher initial depressive symptom scores; 4) a chronic trajectory with moderate initial severity; and 5) a chronic trajectory with severe initial severity. Because the two improving trajectories, as well as the two chronic trajectories, were very similar and for the purpose of increasing power, we combined these pairs, yielding three course trajectories: 1) MDD-remitted (REM), showing a rapid remission of symptoms ($n = 59$); 2) MDD-improved (IMP), showing a gradual improvement in symptoms from baseline to follow-up ($n = 36$); and 3) MDD-chronic (CHR), showing no relief from symptoms from baseline to follow-up ($n = 23$). See Figure S1 in Supplement 1 for a graphic representation of these symptom trajectories. We emphasize that although these class labels were determined on an overlapping sample, the measures employed to predict them were distinct, thereby avoiding circularity.

Baseline Clinical Predictors

The prognostic value of several baseline clinical characteristics was assessed, including severity of depression using the Inventory of Depressive Symptomatology (IDS) (26), severity of anxiety using the Beck Anxiety Inventory (27), information on duration of depressive and anxiety symptoms before baseline derived from the baseline LCI (assessing the number of months the patient spent with depressive and/or anxiety symptoms 4 years before baseline), age of onset, and years since first episode, plus neuroticism, extraversion, and conscientiousness personality traits from the corresponding scales of the NEO-Five Factor Inventory questionnaire (28). Additionally, childhood trauma (before age 16) was measured by structured interview and indexed from 0 to 8, as used previously (29). These measures to predict MDD course were all independent from the measure that was used to define the course trajectory groups (i.e., burden of depressive symptom scores derived from the LCI, which was assessed at 2-year follow-up).

Functional MRI Task Paradigms

Faces Task. An emotional faces paradigm was used to assess brain activation during emotion processing. Color pictures of angry, fearful, sad, happy, and neutral facial expressions, plus a control condition consisting of scrambled faces, from the Karolinska Directed Emotional Faces System (30) were presented. Contrasts used to train the classifier were angry > scrambled faces, fearful > scrambled faces, happy > scrambled faces, and sad > scrambled faces. See Supplement 1 for details.

Tower of London Task. A Tower of London (ToL) task was used to assess brain activity during visuospatial planning.