Imaging biomarkers and biotypes for depression

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A new study identifies four distinct 'biotypes' of depression on the basis of fMRI resting-state functional connectivity in a diverse sample of more than 1,000 individuals. The biotypes are diagnostic of depression and predict treatment response.

Depression, like other mental-health disorders, is a heterogeneous construct defined and diagnosed on the basis of symptoms. These include either depressed mood or anhedonia and a mix of four or more of nine other symptoms, including changes in appetite, sleep, fatigue, concentration, feelings of worthlessness and suicidal ideations[1]. To count as depression, these symptoms may not be caused by 'appropriate' responses to life events and must cause functional impairment. Assessment of the condition, as stated in the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5), "inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms,"[1] which contributes to low diagnostic reliability[2] and the potential for misdiagnosis[3].

However, depression also has a pathophysiology in brain circuits. Although adverse life events, social context and genetic variations can be causal factors in the development of depression, their effects are mediated by the brain. Developing brain-based diagnoses and treatments for depression is a major feature of several modern mental-health initiatives, including the Research Domain Criteria (RDoC) framework[4] and Precision Medicine Initiative[5]. The ultimate goal of these approaches is not to recapitulate diagnostic categories, just as the goal of the germ theory of disease was not to redescribe symptoms in biological terms; rather, it is to develop objective measures of symptom-linked pathophysiology that can lead to new, biologically based categories that are useful for guiding prevention and treatment efforts. The identification of brain measures strongly linked to symptoms and current diagnoses is a crucial initial step—a gateway to understanding the 'depressed brain.' In particular, identifying biotypes—clusters of individuals who have different symptom-linked brain features—might help to better tailor treatments to an individual's specific underlying pathophysiology, as is being done in the fields of infectious disease, cancer and other areas of medicine.

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In this issue of *Nature Medicine*, Drysdale *et al.*[6] take an important step forward by using human neuroimaging to develop biotypes for depression. They collected resting-state fMRI data from 1,188 individuals studied across 17 research sites worldwide (**Fig. 1**). For each individual, they calculated resting-state functional connectivity—intercorrelations of fMRI signal fluctuations—among 258 regions distributed across the brain. Connectivity data were used to identify four biotypes of individuals with depression whose brain-wide patterns of connectivity differed from those of healthy controls in distinct ways.

Early research often assumed that one brain region implements one 'modular' function, but many mental phenomena are now understood to depend on interactions between multiple brain systems. Such phenomena include basic emotional responses, pain, memory, attention, object recognition and others[7,8]. However, finding patterns of connectivity that reliably differentiate patient and control groups has been challenging, in part because of a 'needle in a haystack' problem: a modern fMRI scan allows for the estimation of approximately 60 billion pairwise functional connections.

To identify reliable, depression-related connectivity patterns, Drysdale *et al.*[6] use machine learning, a family of pattern-recognition techniques that is increasingly used in many fields, ranging from cancer genomics to consumer behavior and aerospace engineering[9]. They developed the four biotypes of depression in a closely matched, multisite sample of individuals clinically diagnosed with major depression (n = 220). They optimized the biotypes in a larger training sample that consisted of patients with depression (n = 333) and healthy controls (n = 378) and tested how accurately patients with each biotype were differentiated from controls. Impressively, they tested the final model prospectively in a separate replication sample (n = 477). This last step is crucial for providing unbiased estimates of the model's accuracy. Other studies have claimed to accurately differentiate individuals with depression from controls, but Drysdale *et al.*[6] are the first to replicate a depression versus control classifier in an independent multisite sample.

The biotypes included a common core of altered connectivity in prefrontal, orbitofrontal, posterior cingulate and parahippocampal cortices, and in the thalamus, nucleus accumbens and pallidum. But each biotype was associated with a distinct pattern of symptoms and functional connectivity. Among other relationships, biotypes 1 and 2 are highest in anergia and fatigue, and as compared to healthy controls, they show reduced connectivity with anterior cingulate and orbitofrontal cortex. Biotypes 3 and 4 are high in anhedonia and psychomotor slowing and show increased thalamic and frontostriatal connectivity. Biotypes 1 and 4 are high in anxiety and abnormal in fronto-amygdala connectivity. The biotype classifications were stable across 4–6 weeks (n = 50). And, impressively, each depression biotype was differentiable from controls with ~80–90% sensitivity and specificity.

The stratification of patients on the basis of biological measures enabled Drysdale *et al.*[6] to tackle several interrelated goals related to the RDoC and Precision Medicine initiatives. First, it provides a step toward the personalization of treatment. Drysdale *et al.*[6] used their biotypes to predict treatment response to dorsomedial prefrontal cortical (dmPFC) transcranial magnetic stimulation, an emerging treatment for depression (n = 124). Stimulation was most effective for biotypes 1 and 3 (83% and 61% responded to treatment, respectively), but less so for biotypes 2 and 4 (25–30% responded). An individual's biotype, combined with other connectivity features, differentiated responders from nonresponders with 90% accuracy, whereas prediction of treatment response on the basis of clinical symptoms alone was much less accurate (63%). An independent replication (n = 30) showed 88% accuracy for brain-based prediction of treatment response.

Drysdale *et al.*[6] also tested their framework on individuals with either generalized anxiety disorder (GAD) or schizophrenia to identify transdiagnostic brain features that contribute to multiple disorders. GAD, but not schizophrenia, overlaps symptomatically with depression. Drysdale *et al.*[6] found that functional connectivity in the brains of patients with GAD (n = 39) was also similar to that seen in depression. Their model assigned 69% of patients with GAD to one of the depression biotypes, particularly high-anxiety biotype 4. By contrast, only 10%

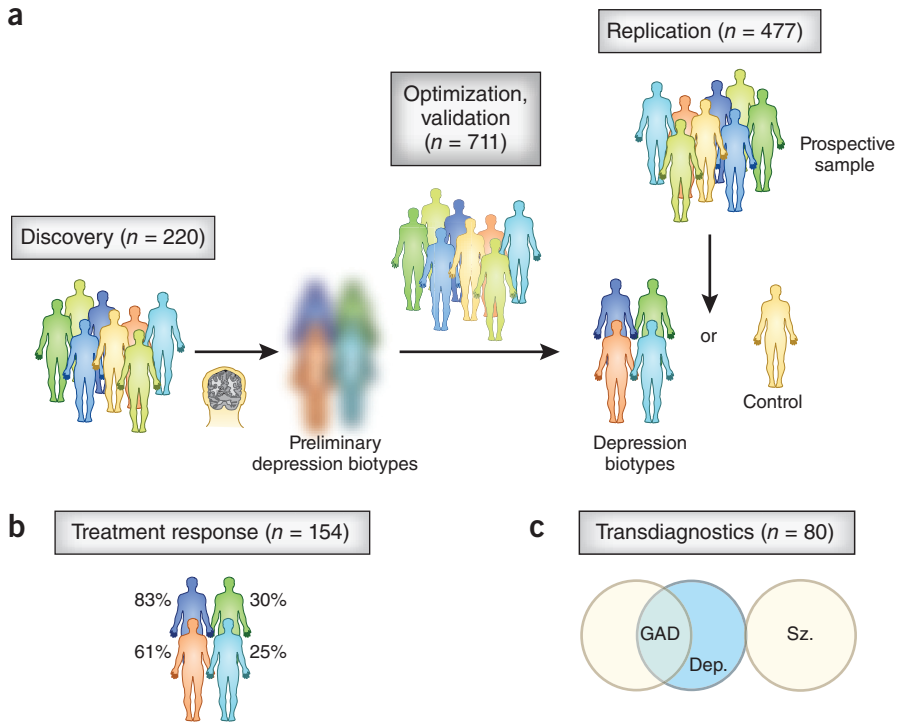

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Figure 1 Biotypes and biomarkers for depression. (**a**) In a discovery sample, Drysdale *et al.*[6] identified fMRI-imaging depression biotypes on the basis of patterns of functional connectivity, first by using canonical correlation analysis (CCA) to relate patterns of brain connectivity with symptom profiles, and then by clustering these individuals according to these connectivity patterns or components. The biotypes were further optimized and accuracy was tested through cross-validated analysis ($n = 711$) and in an independent replication sample ($n = 477$). (**b**) Biotypes predicted response to dorsomedial prefrontal cortex (dmPFC) transcranial magnetic stimulation (TMS) treatment for 154 individuals with depression. (**c**) Biotypes of depression (dep.) overlapped with generalized anxiety disorder (GAD) but not schizophrenia (Sz.).

of patients with schizophrenia matched a depression biotype. These findings demonstrate convergent and discriminative validity among patient groups.

The work by Drysdale *et al.*[6] is part of a growing movement to identify biomarkers for all types of clinical disorder, including dementia, movement disorders, autism, schizophrenia and chronic pain. Their findings suggest that depression will never boil down to dysfunction in one key area that can then be targeted using psychosurgery or brain stimulation. More complex models are required, but such models are also more difficult to understand. We must work hard to develop ways of both validating and understanding the biotypes and other complex brain patterns identified by Drysdale *et al.*[6]. The prediction of treatment response should be replicated and extended to other types of treatment, including pharmacotherapy and psychotherapy. Relating the biotypes to other large-scale networks will help us to understand their relationships with neurological functions. Testing how they relate to mental processes—e.g., attention, memory, emotion and social cognition—will help us to understand their psychological import. Manipulation of these networks in humans and homologous networks in other species, for example, via opto- and pharmacogenetics, will help us to understand their these networks' causal relationships with symptoms and other mental processes. With continued work, we see tremendous potential for the biotypes of Drysdale *et al.*[6] for understanding, treating and preventing depression and other mental-health disorders.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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