Biological Psychiatry

Risks for Major Depression: Searching for Stable Traits

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In this issue of *Biological Psychiatry*, Scifo *et al.* (1) follow a reasonable clinical and epidemiologic classification to separate biological traits and states. They base their hypothesis on existing strong findings that patients often have lifelong recurring episodes of major depression of increasing severity, shorter remission periods, and reduced therapeutic response. Based on these observations, they reason that patients with differing clinical courses (single episodes, single episodes in remission, recurrent episodes, recurrent episodes in remission, and control subjects) should show differing biological traits and states.

Applying mass spectrometry–based proteomics to postmortem tissue, they tested 3630 proteins within the subgenual anterior cingulate cortex, a region previously implicated in the modulation of negative mood and found to be responsive to deep brain stimulation in patients with treatment-refractory depression (2). They identified 98 proteins whose expression was associated with major depressive disorder (MDD). Much to their surprise, they found weak evidence of proteomic differences as a function of depressive state. Instead, they found persistent effects of MDD independent of episode or remission, demographic characteristics, or other clinical measures of severity. They concluded that these proteomic differences did not predict state differences, but may have predicted traits. These depression effects were detected in a host of proteomic measures that certainly will guide numerous other investigations.

One might get lost in the weeds of this study and argue that even an independent committee of experienced clinicians, using a range of clinical and research data, as they had, could not really discern the long-term clinical course upon which their classification rested. Other clinical features might have been included, such as age of onset, episode duration, treatment resistance, and familial risk. It is even possible that some of the healthy control subjects who never had depression carried a familial risk for it. This methodological diversion, while appropriate for future hypothesis testing, would miss the forest of their findings and divert from their potential to inform the development of biomarkers of depression as a trait.

Trait markers, sometimes referred to as endophenotypes, are abnormalities that 1) precede the onset of the disorder and are distinct from biological changes that occur as a result of the disorder and 2) are stable over time (3). These are difficult criteria to meet and may be nearly impossible to achieve using postmortem samples.

Other approaches to finding traits in living human samples using these criteria have been tried. We previously reported on a potential biomarker for depression vulnerability in a three-generation study of MDD. Because of the high-risk design, individuals at risk could be studied before they became ill, so we partially handled the first criterion (4). We found that second- and third-generation offspring at high compared with low familial risk for MDD (where we defined familial risk based on the presence or absence of MDD in the first-generation probands) had thinner cortices, particularly in the lateral surfaces of the right hemisphere. The thinning was present even in offspring who were at risk but who had never had an episode of MDD, suggesting that it was unlikely to be a consequence of the illness. We hypothesized that the cortical thinning may represent an endophenotype for the familial form of MDD (5).

We could not initially test the second criterion. Was this putative trait stable? While there have been several studies testing the reliability of brain measures in the short term, testing long-term stability requires individuals to be imaged over long periods of time (increasing the risk of sample attrition) while accounting for changing imaging methods on the one hand and the naturally occurring effects of age and clinical course on the other. These are cumbersome requirements. To test stability of the presumed trait, we rescanned 82 second- and third-generation offspring from the high-risk population approximately 8 years after the initial scan and found that both individual-subject level absolute cortical thickness and thickness differences between the high- and low-risk groups were stable 8 years later (6). Notably, the thinning was stable despite changes in magnetic resonance imaging platform and field strength (from a Sonata 1.5T [Siemens, Erlangen, Germany] and a Signa 3T [GE Healthcare, Chicago, IL]). The study provided evidence for cortical thinning as a possible stable trait biomarker for familial vulnerability for depressive illness, and supports the ability to detect persistent and clinical relevant anatomical findings regardless of magnetic resonance imaging platform.

We have since documented similar stability of individual posterior electroencephalography alpha patterns across an even longer (10-year) period (7). This study, while demonstrating stability of a trait, has not tested that the trait is related to familial depression.

An independent treatment study, Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care, which included 170 patients with current moderate/severe depression and 52 never-depressed patients, supported the lack of state findings for cortical thickness (8). Perlman *et al.* (8) found that cortical thickness was not associated with current MDD and did not differentiate currently depressed patients from nondepressed healthy control subjects. While cortical thickness did not appear to be a state

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marker, we could not determine that it was a trait. This study demonstrated a potential limitation in searching for biomarker traits in currently ill patients and control subjects without more information about their family history and course. There are of course multiple ways to determine stable trait markers. Recent studies have tried to statistically disentangle trait versus state effects by parsing out stable from unstable variance (9). These methods are currently applied to clinical data, but further development to allow testing of more complex imaging modalities is needed. Such studies would also need to be long-term. For disorders such as MDD, clinical states can themselves last for long periods of time, leading to potential misclassification of states as traits.

Postmortem studies are difficult to carry out and may preclude the testing of marker stability (10). They would require following large samples of patients over time with permission for postmortem studies. However, postmortem studies can be far more informative because they allow direct assay of potential molecular pathology. How can their findings be translated into in vivo techniques? Can the stability of proteomic correlates in the living brain be examined with noninvasive techniques, such as magnetic resonance spectroscopy?

The main results presented by Scifo *et al.* (1) point out the presence of persistent MDD effects on proteomic measures related to presynaptic neurotransmission, synaptic function, cytoskeletal rearrangements, energy metabolism, phospholipid biosynthesis/metabolism, and calcium ion homeostasis. In vivo magnetic resonance spectroscopy, on the other hand, measures metabolites, such as choline-containing compounds (making cell membranes), creatine (involved in energy metabolism), gamma-aminobutyric acid (a major inhibitory neurotransmitter), as well as inositol, glucose, *N*-acetylaspartate, alanine, and lactate.

Applying magnetic resonance spectroscopy in living subjects who are chosen possibly based on family risk and clinical course may be a reasonable next step to examine the stability of correlates, or proxies, of the postmortem proteomics (e.g., glutamate/glutamine levels). Scifo *et al.* (1) have provided many new avenues for research.

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