This Is Your Brain. This Is Your Brain on Treatment. Any Questions?

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This month's *Journal* features an article by Pavuluri and colleagues[1] that may herald the future of clinical practice, whereby treatment development is guided by brain imaging.

Specifically, Pavuluri and colleagues sought to evaluate the effect of risperidone or divalproex on brain circuits mediating affect and working memory in children and adolescents with bipolar disorder (BD). To achieve this goal, they randomized youths with BD to receive risperidone plus placebo or divalproex plus placebo and conducted pre- and post-treatment functional magnetic resonance imaging (fMRI) scans.

The study's main finding was a differential effect of treatment on fMRI outcomes but not on clinical outcomes. Specifically, compared with the divalproex group, the risperidone group, irrespective of treatment response, had a greater change in the activation of the left ventral striatum—an area rich in dopamine-2 receptors that mediate reward processing. In contrast, the divalproex group, irrespective of treatment response, had a greater activation in the left inferior frontal gyrus and right middle temporal gyrus—areas implicated in attention and memory. This suggests the possibility that medications may be used in a personalized medicine approach to target precise cognitive or emotional processes gone awry in a particular patient with BD.

Participants included 21 youths with BD (13.6 ± 2.5 years old) who were in a manic or mixed mood state. After a 1-week medication washout period (4 weeks for fluoxetine or aripiprazole), participants with BD underwent scanning and were randomized to either treatment arm.

Treatment response was defined as an improvement of at least 50% in the Young Mania Rating Score. At the end, the risperidone dose was 1.35 ± 0.46 mg/day in the responders (six of 10) and 1.45 ± 0.35 mg/day in the nonresponders (four of 10). The divalproex dose was 852.14 ± 275.13 mg/day in responders (4 of 11) and 866.67 ± 214.52 mg/day in nonresponders (7 of 11). Ninety-five percent of the divalproex group achieved a serum valproate level higher than 75 μg/mL by the fifth day.

At baseline and the end of the trial, participants completed a 7-minute fMRI scan paired with a two-back working memory task. Specifically, angry, happy, or neutral faces were presented for 3 seconds each in blocks of 10 faces of the same type. Participants pressed a button if they saw the same face presented two trials previously. Between face-type blocks, participants had 20 seconds of rest for their brain activity to return to baseline. Typically developing controls (n = 15; 14.5 ± 2.8 years old) were recruited and underwent scanning twice as a baseline reference for the fMRI data.

The results indicated that the risperidone treatment was associated with alterations in striatal activity, whereas the divalproex treatment was associated with alterations in frontal and temporal activities. What does this mean for practitioners—now and in the near future? Two points are worth comment.

First, combining neuroimaging and treatment methods in the same study holds the potential to advance the understanding of how current treatments work by identifying the predictors of response (or nonresponse) and clarifying the cognitive and emotional processes underlying specific psychiatric disorders that could be used as targets for novel treatments. This is the same mechanistic biomarker approach that has yielded such success in cancer chemotherapy, most notably pediatric-onset acute lymphoblastic leukemia, where biomarkers gleaned from tissue samples have transformed the 5-year survival from nil to around 85% in only a few decades.[2,3]

Extrapolating to the extreme from the present study—and needing additional research—it is

possible that, in the future, youths with BD whose pretreatment scans indicate abnormal reward processing may be treated with risperidone to address their aberrant neurocircuitry or those whose pretreatment scans indicate that impaired attention and memory might be treated with divalproex. We are not there yet, and anyone promising that now is far over-reaching the bounds of the data. However, studies similar to that by Pavuluri and colleagues have begun to elucidate the neural mechanisms of treatment not only in pediatric BD[4-6] but also in children or adolescents with anxiety,[7,8] depression,[9] or attention-deficit/hyperactivity disorder.[10,11]

Moreover, this approach is not the exclusive province of medication trials. Studies pairing imaging and nonpharmacologic treatment have examined the effects of cognitive behavioral therapy, such as a study of adolescents with obsessive-compulsive disorder.[12] This approach has also recently been used to study cognitive remediation, for example, in adults with schizophrenia.[13] In the future, such studies may lead to the elucidation of neural markers of treatment response (or nonresponse) that would guide a selection of nonmedication or medication treatments in a personalized medicine approach common to cancer treatment.

Second, it is important to note that such studies are becoming increasingly difficult to conduct. Either methodology is expensive on its own, but the combination of a clinical trial plus neuroimaging requires significant resources at a time when research funding remains flat or in decline. Although this study was supported by the National Institutes of Mental Health, this may be more difficult in the future. Thus, future studies will require transparent and ethical collaborations between academia and the pharmaceutical industry, because drug development in the United States is primarily a private-sector venture. Unfortunately, there have been too many recent examples of such relations gone awry that not only attract media attention but also erode patients' trust. However, without such partnerships done right, we will remain stuck with the same treatments.

Thus, our profession's progress to improve treatment options hinges on our ability to do this task, to navigate these collaborations successfully, today. This article suggests that we can provide better, more data-driven treatments—today and in the future. &

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