Imaging Adolescent Depression Treatment

In this issue of the *Journal*, Tao et al. (1) report the first results from a neuroimaging study examining the neural circuitry in adolescents with depression before and after treatment. This type of research has been greatly needed in a field in which most imaging studies of depression (especially with regard to treatment) have been conducted in adults. Because of ongoing brain development during adolescence, the neural mechanisms that underlie the disorder could be distinct. Similarly, the mechanisms underlying treatment response in adolescents may be different from those in adults, given increased neuroplasticity during the adolescent period. Furthermore, examination of these mechanisms during early phases of the disorder provides the opportunity to avoid confounds due to complex treatment histories or potential scarring from years of disease. Most important, a better understanding of adolescent-specific mechanisms will be a critical foundation for the advancement of early interventions, which could significantly affect public health.

Appropriate for this first effort, Tao et al. chose to investigate treatment mechanisms using a standard intervention: fluoxetine. Using fMRI, the authors examined neural responses to fearful facial expressions in nonmedicated adolescents with depression and in healthy comparison subjects at baseline, and then they repeated the measures after an 8-week period in which the depressed group received treatment with fluoxetine. The key findings are that 1) prior to treatment, greater neural responses to fear in both limbic and cortical regions were observed in the depressed adolescents, and 2) these group differences abated after treatment (i.e., normalization).

Research studies such as this—that collect brain imaging data along with clinical treatment—can potentially provide several types of biomarkers: diagnostic markers, treatment outcome predictors, markers of disease progression, and markers of neural changes that result from treatment. Tao et al. confirm previous findings from studies of both adults (2, 3) and adolescents (4, 5) with depression that have reported elevated activation in the amygdala during the processing of fearful faces. While it is reassuring that this finding is replicable, the utility of fMRI as a diagnostic biomarker for adolescent depression based on these results is limited, since this pattern of increased activation in the amygdala is also observed in other psychiatric populations. Arguably, the application of fMRI as a diagnostic biomarker is less of a practical goal for the management of adolescent depression, which is common and relatively simple to diagnose using existing clinical tools. Rather, the greater value of these initial findings lies in advancing the current understanding of the neural mechanisms that underlie adolescent depression and in providing the groundwork for research that tests how treatment affects these abnormalities.

The most exciting aspect of this study is that it represents a first step toward developing biomarkers that delineate change resulting from treatment. Tao et al. report that the group differences that were present before treatment with fluoxetine were no longer present after treatment. This finding is important for two reasons.

This article is featured in this month's AJP **Audio**

First, from a clinical perspective, as the authors point out in the discussion section, this research provides a powerful message that clinicians can give to families: adolescents with depression have abnormal neural circuitry, and treatment with fluoxetine will make the circuitry normal again. Second, from a research perspective, this finding is an initial step supporting this fMRI approach for illustrating the relevant circuitry and potential mechanisms of treatment. The next steps will involve delving further to determine the specificity of these changes resulting from treatment: to characterize the overlapping and complementary mechanisms across treatments (i.e., other medications, psychotherapies) and to differentiate effects on circuitry in those who respond to treatment compared with those who do not.

In keeping with other studies of adolescent and adult depression, Tao et al. report that only 60% of the adolescents responded to treatment. However, they do not report whether any baseline imaging parameters predicted response relative to nonresponse, a high demand in the field. This study follows only one previous imaging plus treatment study of adolescent depression, which examined reward-related brain functioning in adolescents with depression before (but not after) treatment with either cognitive-behavioral therapy (CBT) (N=7) or CBT plus a selective serotonin reuptake inhibitor (N=6) (6). Greater striatal activity during reward outcome predicted higher general symptom severity after treatment, whereas greater striatal activation during reward anticipation predicted lower anxiety after treatment (because of the small sample size, the reported results were not specific to treatment type) (6). Results from a larger body of research in adult depression suggest a general pattern: increased baseline resting metabolism or activity in the pregenual anterior

Because of ongoing brain development during adolescence, the neural mechanisms that underlie the disorder could be distinct.

cingulate cortex (Brodmann's area 24) in response to tasks predicts responsiveness to treatment (medication) (7, 8), but increased resting metabolism or activation in the subgenual anterior cingulate cortex (Brodmann's area 25) predicts treatment resistance (medication, CBT) (9, 10). Consideration of these adolescent and adult studies highlights several points. First, fMRI strategies yield differential results, depending on the neural systems they are designed to test (e.g., resting state, threat, mood, reward). Studies that examine multiple systems may be most helpful. Second, imaging plus treatment studies will ideally address both treatment predictors and neural changes that result from treatment simultaneously. Third, larger sample sizes will be needed to delineate the effects on the brain by different types of treatment and to define differences between responders and nonresponders across treatments and age groups.

Although the baseline results for the adolescents in the Tao et al. study generally map to previous findings in studies of adult depression, there are also differences: whereas research on adults has painted a "hypofrontal" picture of *lower* activation and metabolism in dorsal frontal areas in depressed individuals (e.g., reference 3), the voxel-wise analysis of this adolescent study revealed *higher* activation in the depressed group in multiple (uncorrected) clusters within the frontal lobe. In contrast, a recent study reported that youths (ages 16–21 years) at increased familial risk for depression had diminished responses to fearful faces in the left dorsolateral prefrontal cortex (11), which is more consistent with findings in adults. Key factors that may have led to these different results could include sample differences in age (i.e., the at-risk sample was older and closer to adulthood) and illness status

(at-risk compared with currently ill) or differences in the image acquisition/analysis approach. Future research that uses the same methodology simultaneously in examining both adolescents and adults, or both at-risk and affected individuals, will help resolve some of these issues. Furthermore, results from studies with larger samples that can survive statistical correction will allow more firm conclusions than those that can be made from the voxel-wise results in the Tao et al. study.

The findings reported by Tao et al. are exciting and open up new avenues for research. The next steps in this field must strive to disentangle the numerous contributors that likely affect both baseline and posttreatment findings: age at assessment, age at onset of depression, lifetime burden of illness, illness status (e.g., familial risk, first episode, remission, relapse), treatment history, and type of treatment. Addressing these issues through careful research that takes advantage of recent progress in neuroimaging approaches and that uses precision in reporting result locations holds great promise for the field. Mapping out these biomarkers will be the key to enabling the clinical advancements needed to allow patients to achieve remission in the earliest phase of illness, bringing adolescents back on course for healthy development and thus circumventing a host of potential negative consequences over their lifetime.

References

1. Tao R, Calley CS, Hart J, Mayes TL, Nakonezny PA, Lu H, Kennard BD, Tamminga CA, Emslie GJ: Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. Am J Psychiatry 2012; 169:381–388

2. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA: Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 2001; 50:651–658

3. Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME: Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biol Psychiatry 2007; 61:198–209

4. Beesdo K, Lau JY, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, Fromm SJ, Goldwin MA, Wittchen HU, Leibenluft E, Ernst M, Pine DS: Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry 2009; 66:275–285

5. Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Max JE, Bischoff-Grethe A, Lansing AE, Brown G, Strigo IA, Wu J, Paulus MP: Adolescents with major depression demonstrate increased amygdala activation. J Am Acad Child Adolesc Psychiatry 2010; 49:42–51

6. Forbes EE, Olino TM, Ryan ND, Birmaher B, Axelson D, Moyles DL, Dahl RE: Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. Cogn Affect Behav Neurosci 2010; 10:107–118

7. Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, Bullmore E: Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol Psychiatry 2007; 62:407–414

8. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT: Cingulate function in depression: a potential predictor of treatment response. Neuroreport 1997; 8:1057–1061

9. Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS: Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. J Psychiatry Neurosci 2009; 34:175–180

10. Siegle GJ, Carter CS, Thase ME: Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry 2006; 163:735–738

11. Mannie ZN, Harmer CJ, Cowen PJ, Norbury R: A functional magnetic resonance imaging study of verbal working memory in young people at increased familial risk of depression. Biol Psychiatry 2011; 67:471–477

KATHRYN R. CULLEN, M.D.

From the Department of Psychiatry, University of Minnesota Medical School, Minneapolis. Editorial accepted for publication January 2012 (doi: 10.1176/appi.ajp.2012.12010057). Address correspondence to Dr. Cullen (rega0026@umn.edu).