Severe Irritability in Youths: Disruptive Mood Dysregulation Disorder and Associated Brain Circuit Changes

As psychiatrists, we treat syndromes that we don't deeply understand. The boundaries and thresholds for treatment are unclear, though improving (1). We have hypotheses about the pathophysiology of many disorders, and recently developed approaches may help us make greater progress (2, 3), but we have far to go. Patients with strongly impairing and long-lasting disorders come to us fitting or nearly fitting diagnostic criteria for many disorders or impaired but not perfectly fitting criteria for the disorder they seem to have. Despite the limitations of our diagnostic schemas and our understanding of mechanisms, we need to treat them.

School-age children with impairing tantrums, together with irritable, depressed, and sometimes euphoric mood, suffering severe impairment in their families and in social and school functioning, are well known to child psychiatrists. They are frequently thought to have a syndrome related to bipolar disorder and frequently treated with atypical antipsychotics.

DSM-5 included a new diagnosis, disruptive mood dysregulation disorder, which was added "in order to address concerns about the potential for the overdiagnosis of and treatment for bipolar disorder in children" (1). Diagnostic criteria for this diagnosis require severe temper outbursts, on average three or more times per week, irritable mood most of the day nearly every day, and never having had a distinct period of 1 day or more meeting full criteria (other than the duration criteria) for a manic or hypomanic episode. This diagnosis arose from previous work of a single group that proposed a similar but somewhat different syndrome, severe mood dysregulation, which additionally requires the presence of hyperarousal symptoms not required in the criteria for disruptive mood dysregulation disorder (4, 5). Because of the limited data available, the inclusion of this new diagnosis in DSM-5 has been contentious. A recent examination of disruptive mood dysregulation disorder in previously collected epidemiologic samples (6) found rates to be 3.3% in a preschool sample and 1.1% and 0.8% in two samples of older youths. In those samples, most youths with disruptive mood dysregulation disorder had other comorbid psychiatric disorders, particularly oppositional defiant disorder (odds ratio range, 63–103). The DSM-5 field trials found modest test-retest reliability of disruptive mood dysregulation disorder (kappa=0.25, judged to be in the "questionable" range) (7), although this was similar to the kappa of 0.28 found for major depressive disorder in the same trials. While the criteria for disruptive mood dysregulation disorder were broadly based on those for severe mood dysregulation, there is substantial nonoverlap between youths identified by these two different syndromes.

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The disruptive mood dysregulation disorder diagnosis appears to separate out youths with chronic irritability who ultimately have low risk for developing bipolar disorder (8). In contrast, as found in the bipolar disorder not otherwise specified research criteria used in the Course and Outcome of Bipolar Youth collaborative study, youths who do not meet duration criteria for bipolar disorder but have significant periods of manic or hypomanic symptoms and other bipolar disorder symptoms do seem to be at greatly elevated risk for full bipolar disorder over time (8).

In this issue of the *Journal*, Deveney et al. (9) report a comparison between 19 youths with severe irritability who met criteria for both severe mood dysregulation and disruptive mood dysregulation disorder and 23 healthy comparison youths. The authors define irritability as a low threshold for experiencing negative affect in response to frustration (i.e., blocked goal attainment). They used a Posner spatial cuing functional MRI (fMRI) task with monetary rewards on some trials. Frustration was induced by telling participants that they were responding too slowly. There were equal numbers of trials on which participants could earn or lose 50 cents ("money" trials) and trials on which there was no monetary reward or penalty ("no-money" trials). During the frustration block, participants were told that they were "too slow" on 60% of the correct response trials (negative feedback) and informed that they won money or did a "good job" on the other 40% (positive feedback). Youths with severe mood dysregulation reported more frustration than healthy youths after the last two runs of the affective Posner task.

Previous fMRI studies of circuitry mediating frustration in adults and youths found increased activation with frustrating stimuli in regions including the amygdala, parietal attentional networks, and dorsal and ventromedial prefrontal areas. Thus, in the Deveney et al. study, differences in these areas between youths with severe mood dysregulation and healthy youths in response to frustration were hypothesized, as were differences in ventral striatal response, given the striatal activation when an expected reward is not received (negative prediction error).

In the region-of-interest analyses, youths with severe mood dysregulation exhibited less activation in the left amygdala and left and right striatum than healthy youths on negative feedback trials but not on positive feedback trials. Youths with severe mood dysregulation also exhibited less activation in the striatum during negative compared with positive feedback trials, while in healthy youths, striatal activation did not differ between positive and negative feedback trials.

In the whole-brain analyses, youths with severe mood dysregulation exhibited less activation in parietal, parahippocampal, and thalamic/cingulate/striatal regions than healthy youths on negative feedback trials but not positive feedback trials. The severe mood dysregulation group was slower than the healthy comparison group on trials in which the stimuli were presented in the box opposite from the cue, showing more difficulty shifting spatial attention away from the cue.

In summary, youths with severe mood dysregulation exhibited markedly decreased activation of neural regions associated with spatial attention, reward processing, and emotional salience after negative feedback (frustrating) trials. In contrast to expectations, this study did not find group differences in prefrontal regions, and the authors theorize that because of the small sample size, this could simply be a type II statistical error. As the authors point out, this constellation of findings may be related to the chronic irritability in disruptive mood dysregulation disorder, the required hyperarousal in severe mood dysregulation, the irritability

across diagnostic groups, or, conceivably, the highly comorbid attention deficit hyperactivity disorder seen in the sample.

What is particularly interesting and important about this study and approach? First, of course, the authors have picked a problem associated with high morbidity and current diagnostic uncertainty, a very important clinical area. And they have found a pattern of brain responses that appears different, and this finding will allow exploration of this particular pattern in irritability in a wide range of other psychiatric disorders.

In addition, this study may serve as a great example of how to make progress thinking about the relationship between specific symptoms, rather than current categorical diagnoses, and brain function in youths. The Research Domain Criteria initiative (2, 3) proposes starting from neural systems responsible for implementing the primary behavioral functions of the brain and considering psychopathology in terms of disruptions of these systems. It emphasizes dimensional approaches rather than categorical approaches and developing measures that work across full dimensional ranges, not just normal or pathological ranges. Broad sampling frames including subjects who do not fall within traditional diagnostic borders are explicitly included (2).

The argument that we can further progress by starting from neural underpinnings and working toward psychiatric symptoms and syndromes is compelling. However, there are many different stages of development, so there are important areas where our knowledge of brain systems during development is sketchier than our understanding of the adult rat, monkey, or human. In addition, human developmental understanding of neural systems is constrained because some informative approaches (e.g., positron emission tomography) are not usable in normal youths, and there are very few brains of children and adolescents in available brain banks. So starting from important symptoms (e.g., irritability) and working toward neural systems while incorporating the other Research Domain Criteria approaches (e.g., full range of symptom levels from normal to impaired, wide range of diagnoses, multilevel assessments, and dimensional rather than categorical measures) may be an important strategy in future studies of irritability and other symptoms that span multiple disorders.

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