



Understanding, Evaluating, and Treating Disruptive Mood Dysregulation Disorder in Childhood

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Sam obtained his Ph.D. in School Psychology from the University of Utah and is licensed as a Psychologist and Certified School Psychologist in the State of Utah. He is also board certified as a Pediatric Neuropsychologist and listed in the Council for the National Register of Health Service Providers in Psychology. He is a Fellow of the American Psychological Association and the National Academy of Neuropsychology. Sam is an Adjunct Assistant Professor in the Department of Psychiatry at the University of Utah School of Medicine. He has authored, co-edited, or co-authored over 50 clinical and trade publications, three dozen chapters, nearly three dozen peer-reviewed scientific articles, and eight psychological and neuropsychological tests. He is in development for a behavioral assessment tool to evaluate DMDD and is editing a clinical volume about DMDD. Sam is the Editor in Chief of the *Journal of Attention Disorders*. Since 1980, he has served as the Clinical Director of the Neurology, Learning, and Behavior Center in Salt Lake City, Utah.

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Objectives

Following this presentation, you will:

- possess an understanding of the evolution of the DMDD diagnosis.
- understand and be able to apply the DSM-5 criteria for DMDD.
- know how to integrate various assessment methods in a comprehensive evaluation for DMDD.
- have a method for differential diagnosis and assessment of comorbidity.
- appreciate the emerging methods of treatment for DMDD.
- be in possession of multiple resources to learn more about DMDD.

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Three Youth: Lucy

- Lucy is 10 years old. She was a colicky and excessively restless, irritable toddler who was active, fidgety, and had difficulty sitting still.
- She demonstrates extremes of emotion. She exhibits frequent tics, including blinking, wiggling her stomach, pushing her stomach in and out, grabbing underwear away from her crotch, and swallowing excessively.
- She demonstrates rigidity with bedtime routines and diet.
- She interprets conversation literally and appears to struggle to understand basic social behaviors.



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Three Youth: Lucy (cont.)

- She had been diagnosed with an unspecified anxiety disorder, attention-deficit/hyperactivity disorder – combined type (ADHD-C), and moderate tic disorder.
- Lucy is currently prescribed a combination of guanfacine, citalopram, and trazodone to facilitate sleep.
- On the Millon Pre-Adolescent Clinical Inventory (M-PACI), Lucy endorsed a significant number of problematic thoughts, feelings, and behaviors at a rate higher than 96% of children of her age. Youth with Lucy's emerging personality style typically demonstrate intense and evocative emotions.
- Lucy presents a triad of significant emotional distress, upsetting thoughts, and worry. She experiences social problems; is defiant, oppositional, inattentive, and hyperactive; and presents with multiple depressive and anxious symptoms.
- Neuropsychological abilities were measured in the average range with slightly weak sequencing.

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Three Youth: Lucy (cont.)

- Working memory, cognitive processing speed, and efficiency were also measured in the average range.
- Lucy demonstrated average vocabulary and verbal comprehension.
- Verbal memory was assessed as average.
- Lucy struggled on a number of visual memory tasks, with visual memory measured as well below average.
- On a continuous performance measure, Lucy had difficulty sustaining attention and with timely responding.
- Motor and perceptual abilities were measured as well below average.
- Lucy's basic reading, math, and written language knowledge were assessed within the average range. Lucy demonstrated a significant weakness in reading comprehension that appeared consistent with her challenges with sentence reading fluency.

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Three Youth: Shane

- Ten-year-old Shane is struggling academically, emotionally, and developmentally.
- He is immature socially.
- At home he is quick to be oppositional and defiant. He has a history of extreme emotional outbursts to the point of passing out.
- He has been evaluated and diagnosed in the past with ADHD-C and oppositional defiant disorder.
- He will steal impulsively.
- He has demonstrated a low emotional threshold and a high intensity of reaction from a very young age. Currently he is able to better recover from these outbursts, but in the past, it could take him up to an hour to recover.



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Three Youth: Shane (cont.)

- He fails to appreciate the disruptive nature of his behavior. He has been a repeat offender. He knows what to do but does not do what he knows consistently. He does not appear to use thought often to guide his behavior. His symptoms appear to be worsening.
- He is rigid and increasingly defiant.
- Although he is taking multiple psychiatric medications, current parent reports note significant behaviors for Shane's age related to emotional distress, upsetting thoughts, worry, social problems, defiant and aggressive behavior, academic challenges, inattention, hyperactivity, impulsivity, depression, and anxiety.
- In contrast, at school Shane appears to function somewhat better. His teacher notes significant challenges academically, patterns of significant inattention, and anxiety.
- Parent and teacher responses for an instrument designed to assess behaviors related to autism spectrum disorder noted significant challenges with social communication, self-regulation, and unusual behavior.

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Three Youth: Shane (cont.)

- On an instrument designed to assess behaviors related to executive functioning, parents and teacher note significant problems with somewhat better functioning at school than at home. Nonetheless, in both settings Shane struggles with attention, inflexible behavior, initiation, organization, planning, self-monitoring, and working memory.
- The primary difference between home and school is that at school Shane is described as demonstrating adequate emotional regulation.
- Assessment placed Shane's neuropsychological abilities in the borderline range. He struggles with planning, simultaneous processing, attention, and sequencing.
- Working memory was assessed at only the 2nd percentile. This combination of neuropsychological weaknesses leads to impairment in Shane's short-term working memory and cognitive efficiency.
- Verbal comprehension was assessed at only the 5th percentile with equally low vocabulary. Memory was assessed at the 12th percentile.

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Three Youth: Shane *(cont.)*

- On a continuous performance measure, Shane was able to pay attention but was markedly impulsive.
- Motor and perceptual abilities appear in the low average to average range.
- Shane is multiple grades behind academically, demonstrating markedly better word reading than reading comprehension. This is consistent with his current pattern of verbal comprehension and neuropsychological abilities. Math was assessed in the borderline range, and written language as well as spelling was low average. Shane's overall academic achievement appears multiple grades below his current placement.

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Three Youth: Adam

- Adam has a history of diagnosis and treatment for attention-deficit/hyperactivity disorder; major depressive disorder recurrent, episode moderate; specific learning disability with impairment in reading comprehension and mathematics.
- Concerns were raised that he may be struggling with other challenges as well.
- He appears defiant and at times depressed.
- He also appears to be "addicted" to electronics.
- Adam fidgets and has difficulty remaining seated.
- He is easily distracted.



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Three Youth: Adam *(cont.)*

- Adam has difficulty sustaining attention. He shifts from one incomplete activity to another.
- Adam has a history of frustrating easily, temper outbursts, and extended tantrums from a very young age. His moods are frequently negative and withdrawn.
- Adam has trouble falling asleep, but then sleeps through the night.
- He is currently taking fluoxetine, guanfacine, and quetiapine in the morning.
- His treating psychiatrist is considering a trial of Strattera.
- Adam also has a history of picking behavior.
- He is rivalrous with siblings.
- He has destroyed property at home when upset. He appears only driven by something that has a personal payoff for him; otherwise, he does not respond well to consequences. Parents have tried, without success, a variety of disciplinary procedures as Adam has matured.

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Three Youth: Adam *(cont.)*

- Neuropsychological abilities were assessed in the average range with superior simultaneous or critical thinking and above-average sequencing. The former typically predicts a level of general comprehension. The latter predicts the acquisition of basic academic knowledge.
- Adam also demonstrated above-average planning but below-average attention to detail. Short-term working memory was assessed within the average range with cognitive efficiency and perceptual speed assessed as below average.
- On an abstract measure of word reasoning, Adam performed at the 84th percentile.
- In contrast, memory scores were impaired with marked weakness noted in verbal memory.

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Three Youth: Adam *(cont.)*

- Adam had taken his prescribed medications on the day of the assessment. On a continuous performance measure, he was able to pay attention but demonstrated a pattern of impulsive responding.
- Motor and perceptual abilities were measured in the low-average to above-average range.
- A brief screening of achievement was consistent with past assessment, reflecting strong academic knowledge.



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What do Lucy, Shane, and Adam have in common?

- An early history of extreme emotional dysregulation and irritability.
- Past diagnoses of ADHD, adverse mood, and disruptive behaviors.
- Refractory to multiple classes of medication, often in combination.
- Social pragmatic and related problems.
- Family members with mood disorders.
- Broad variation in abilities and achievement.



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All three met DSM-5 diagnostic criteria for DMDD following a thorough assessment!

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Overview

- Disruptive mood dysregulation disorder (DMDD) was introduced as a new diagnostic entity under the category of depressive disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).
- It was included in DSM-5 primarily to address concerns about the misdiagnosis and consequent overtreatment of bipolar disorder in children and adolescents. DMDD does provide a place for a significant percentage of referred children with severe persistent irritability that did not fit well into any DSM 4th edition (DSM-IV) diagnostic category.



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Overview (cont.)

- DMDD has been a controversial addition to the DSM-5 due to lack of published validity studies, leading to questions about its validity as a distinct disorder.
- The ICD-10-CM contains a diagnostic category, Persistent mood (affective) disorder, unspecified. It went in to effect on October 1, 2021.
- It includes the American ICD-10-CM version of DMDD - other international versions of ICD-10 may differ.
- This Category also includes:
 - Cyclothymic disorder
 - Dysthymic disorder
 - Other persistent mood [affective] disorders
 - Disruptive mood dysregulation disorder
 - Other specified persistent mood disorders
 - Persistent mood [affective] disorder, unspecified

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Disruptive Mood Dysregulation Disorder

- Since the mid-1990s, there have been concerns that mania in children and adolescents presented differently compared to adults.
- Pediatric-onset mania was believed to present as severe irritability with extended periods of very rapid mood cycling within 1 to 3 days versus discrete mood cycles.
- With this broader concept of pediatric bipolar disorder in the U.S., the rate of bipolar disorder diagnosis increased over 40-fold in less than a decade.
- The conceptualization of severe irritability as a form of mania has also been associated with a sizable increase in the use of mood stabilizers and atypical antipsychotic drugs in children.
- Given the potential side effects of these medications and the paucity of long-term safety data in developing children, controversy continued about the diagnostic validity of the broad phenotype of pediatric bipolar disorder.

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Disruptive Mood Dysregulation Disorder (cont.)

- The National Institute of Mental Health (NIMH) proposed a syndrome called severe mood dysregulation (SMD) to promote the systematic evaluation of children with recurrent temper outbursts and a persistent negative mood.
- The DMDD criteria are primarily derived from the SMD with some significant modifications.
- SMD was primarily created to assess if severe non-episodic irritability belongs to the bipolar spectrum disorder. Validation studies of this syndrome were conducted by comparing it to episodic mania (narrow phenotype of bipolar disorder) on longitudinal course, family history of bipolar disorder, and pathophysiology.
- The youth with SMD had extremely high rates (75%) of attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), as well as anxiety disorders (58%).
- SMD, however, was never formalized as a DSM or ICD condition.

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Disruptive Mood Dysregulation Disorder (cont.)

- DMDD differs in several ways from SMD:
 - SMD required recurrent temper outbursts, a persistent negative mood (which, unlike DMDD, includes depressed mood), and the presence of at least three "hyperarousal" symptoms (pressured speech, racing thoughts or flight of ideas, intrusiveness, distractibility, insomnia, and agitation).
 - These hyperarousal criteria were included because it was these symptoms in persistently irritable children that often led to a concern about mania.
 - Also, age of onset for SMD was before age 12 years and the maximum symptom-free period was 2 months.



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Disruptive Mood Dysregulation Disorder *(cont.)*

- In the DSM-5, the DMDD diagnosis has two core criteria: severe, recurrent temper outbursts and chronic non-episodic irritability.
- Despite its novelty, DMDD is the only diagnosis in the DSM-5 Depressive Disorders section that requires childhood onset.
- The DSM-5 specifically states that individuals whose symptoms meet the criteria for both DMDD and ODD should only be given the diagnosis of DMDD.



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DSM-5 DMDD Diagnostic Criteria A–E

- A. Severe, recurrent temper outbursts (verbal and/or behavioral) that are grossly out of proportion in intensity or duration to the situation/provocation.
- B. Outbursts are inconsistent with the child's developmental level.
- C. Occur three or more times/week.
- D. Mood between temper outbursts is persistently irritable or angry most of the day, nearly every day.
- E. Duration is 12 or more months, without a symptom-free interval of 3 or more consecutive months.

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DSM-5 DMDD Diagnostic Criteria F–K *(cont.)*

- F. Symptoms are present in at least two of three settings (home, at school, with peers) and are severe in at least one setting.
- G. Age at onset, either by history or observation, is before 10 years.
- H. Diagnosis should not be made for the first time before 6 years of age or after 18 years.
- I. Full symptom criteria for manic/hypomanic episodes have never been met for longer than 1 day.
- J. Behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by other disorders like dysthymia, autism spectrum disorder, posttraumatic stress disorder, or separation anxiety disorder. Diagnosis cannot coexist with bipolar disorder, intermittent explosive disorder, and oppositional defiant disorder.
- K. Symptoms not due to physiological effects of a substance or a medical or neurological condition.

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DMDD is Not:

- ADHD - A problem of immaturity in developing self-discipline.
- Bipolar disorder – A problem of excessive emotional highs and lows.
- Anxiety – A problem resulting from a lack of confidence in predicting outcome.
- Unipolar depression – A problem resulting from excessive helpless and hopeless feelings.
- ASD – A social pragmatic problem with accompanying problems with self-regulation and atypical interests and behaviors.
- A personality disorder – A behavioral style of interpreting and interacting with the world.
- Fetal Alcohol Spectrum Disorder
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DMDD is not (cont.)

- Oppositional defiant disorder – A problem of resistance.
- PTSD – A problem resulting from trauma.
- Intermittent explosive disorder – A problem resulting in repeated, sudden episodes of impulsive, aggressive, violent behavior or angry verbal outbursts in which you react grossly out of proportion to the situation.
- Reactive attachment disorder - Failure to show an expected range of emotions when interacting with others; failure to show "emotions of conscience" such as remorse, guilt, or regret. Avoiding eye contact and physical touch, especially with caregivers. Two types: inhibited and disinhibited.
- A normal variation of behavior.

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Epidemiology of DMDD

- There have been very few prospective studies on DMDD. However, studies have examined the prevalence of retrospectively diagnosed cases of DMDD or SMD in existing datasets.
- DMDD symptoms are relatively common in referred children, but the full disorder is much less common.
- However, even those with elevated symptoms not meeting full diagnostic criteria experience significant impairment.
- Rates are substantially higher in clinical samples, especially in those with high rates of externalizing disorders and/or mood lability. However, in many cases, even in clinical samples, the temporal stability of the symptoms is low.

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Epidemiology of DMDD (cont.)

- In the Great Smoky Mountains Study sample, the lifetime prevalence rates of DMDD (4.4%) and SMD (3.3%) were comparable.
- Copeland et al., using existing data from three large epidemiological samples including both preschool and school-age cohorts, reported that around half (46%–49%) of school-age youth and around 80% of preschoolers were found to have severe temper outbursts in the last 3 months.
- Among school-age cohorts, the prevalence dropped to 7% when the DSM-5 frequency criterion was applied and dropped further (1.5%–2.8%) with the duration criterion. Using the full DSM-5 DMDD criteria, the prevalence rate declined to ~1%.



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Epidemiology of DMDD (cont.)

- In the preschool cohort, the prevalence rate of DMDD, using the entire DSM criteria except for age of onset, was 3.3%.
- The school-age youth with DMDD experienced significant social impairment (relationship with parents, siblings, and teachers), school suspension, and service use (mental health and general medical), reinforcing the findings from other studies that youth with severe non-episodic irritability are appreciably impaired, even if they do not meet the criteria for bipolar disorder.
- Similar rates of the core DMDD symptoms were found in another population-based sample of 376 children. In a large nationally representative sample of adolescents, the prevalence rate of DMDD was 0.12% using strict criteria for DMDD and increased with relaxation of the mania/hypomania exclusion criterion (0.56%), the frequency criterion (1.71%), or both (5.26%).
- Higher rates have been reported in clinical samples. Axelson et al. found that 26% of children participating in the Longitudinal Assessment of Manic Symptoms (LAMS) study met DMDD criteria. These children were recruited from outpatient clinics and were preselected for the presence of prominent mood lability.

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Epidemiology of DMDD (cont.)

- In a large clinical sample ($N = 911$) of youth aged 5–18 years referred for problems with behavioral outbursts, SMD was the most common (54.4%) diagnosis.
- In a study of 1,593 children with autism, ADHD, and neurotypical development (6–16 years), mothers reported on the frequency of DMDD symptoms. Percentages of children for whom both irritability and temper outbursts were rated as "often or very often" a problem were 45% for autism, 39% for ADHD-combined type, 12% for ADHD-inattentive type, and 3% for neurotypical children.
- In another study, only 25% of adolescents with bipolar disorder met the criteria for a lifetime diagnosis of the DMDD phenotype (excluding criterion of onset before age 10), suggesting that persistent irritability and temper outburst are not a common precursor to adolescent mania.
- DMDD can develop into anxiety disorders or unipolar depression in late adolescence and adulthood.

<https://doi.org/10.1016/j.jad.2020.12.039>

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Epidemiology of DMDD (cont.)

- **Disruptive Mood Dysregulation Disorder in Juvenile Justice**
 - DMDD criteria were met by 3.3 percent of justice-involved youths in a study of nearly 10,000 youths in the Juvenile Justice System.
 - Results from multinomial regression showed that, after adjustment for covariates, those with DMDD had fewer differences compared with those with other mood disorders than did those meeting criteria for DBDs.
 - Consistent with the DSM-5 classification of DMDD as a depressive disorder, those with DMDD shared more characteristics with youths with mood disorders than with those reporting DBDs.
 - Externalizing behaviors leading to justice involvement may overshadow internalizing symptoms of DMDD, but mood-related conditions should be identified and treated in this population (*J Am Acad Psychiatry Law* 46:329–38, 2018. DOI:10.29158/JAAPL.003767-18).

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Epidemiology of DMDD (cont.)

- **COVID 19 Impact on Youth**
 - The consequences of a pandemic and the measures put in place to decrease transmission of COVID-19 have the potential to adversely affect children and youth with mental health disorders and their families, including siblings.
 - Parental anxiety around job loss, economic uncertainty, lack of access to health care facilities and treatment centers and extension of wait-lists for early intervention programs may cripple a caregiver's or parent's ability to cope with the COVID-19 pandemic
 - Recently, an early published study evaluated 1036 quarantined children and adolescents in China in an age range from 6 to 15 years, of which 112, 196, and 68 presented depression, anxiety, and both, respectively.

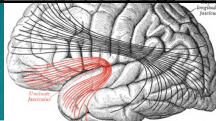
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Epidemiology of DMDD (cont.)

- Another study demonstrated a high prevalence of psychological distress in quarantined children and adolescents due to the COVID-19 pandemic in India. These children experienced helplessness (66.11%), worry (68.59%) and fear (61.98%), compared to non-quarantined children.
- It was also reported in China that children and adolescents aged 3–18 years presented symptoms of inattention, clinging, worry and irritability during this pandemic.
- No studies yet on DMDD and COVID.
- Related materials:
 - doi: [10.1016/j.iad.2021.10.115](https://doi.org/10.1016/j.iad.2021.10.115)
 - doi: [10.1016/j.iad.2020.11.117](https://doi.org/10.1016/j.iad.2020.11.117)

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Neurobiology of DMDD



- Neurobiological models of both BD and DMDD emphasize the relevance of the prefrontal cortex (PFC) and amygdala.
- In contrast to the extensive literature in BD, no study to date has investigated in depth WM microstructure in DMDD.
- In DMDD, one might also expect reduced functional anisotropy (thought to reflect fiber density, axonal diameter, and myelination in white matter) in the anterior Corpus Callosum connecting the prefrontal cortices of both hemispheres and in the uncinate fasciculus (white matter tract) connecting the ventral prefrontal cortex with the amygdala (*J Am Acad Child Adolesc Psychiatry*. 2020 Oct;59(10):1135-1145).

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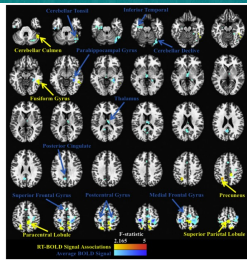


FIGURE 1 Group-by-time point effects on reaction time and blood oxygen level-dependent (RT-BOLD) signal and average BOLD signal. Note: This figure presents the regions that showed a significant group-by-time point interaction predicting RT-BOLD signal relations (amplitude modulation) in yellow and predicting average BOLD activity in blue. Threshold F statistics from the voxel-wise repeated measures analysis of variance are presented. Peak coordinates, voxel extents, and further information about each region are presented in Table 2.

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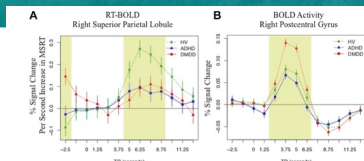


FIGURE 2 Group differences in reaction time and blood oxygen level-dependent (RT-BOLD) signal and average BOLD signal. Note: This figure displays exemplar results illustrating group-by-time point interaction predicting (A) RT-BOLD signal in the right superior parietal lobule and (B) average BOLD signal results in the right postcentral gyrus. In panel A, estimated marginal means of percentage of signal change per second increase in mean standardized reaction times (MSRT) and their standard errors from repeated measures analysis of variance predicting RT-BOLD signal association effects are displayed. In panel B, estimated marginal means of percentage of signal change and their standard errors are presented. In the 2 plots, healthy volunteers (HV; green circles), patients with attention-deficit/hyperactivity disorder (ADHD; blue triangles), and patients with disruptive mood dysregulation disorder (DMDD; red squares) are represented by shading indicating time points that showed a p -value less than .05 indicating significant F -test differences among any of the 3 groups. Stimulus onset is denoted as at 0 seconds; the 2 pre-stimulus repetition times (TRs) modeled are -2.5 and -1.25 seconds.

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Behavioral and Neural Sustained Attention Deficits in Disruptive Mood Dysregulation Disorder and Attention-Deficit/Hyperactivity Disorder

David Pagliaccio, ^{no}, Jillian Lee Wiggins, ^{no}, Nancy E. Adleman, ^{no}, Alexa Curhan, ^{sa}, Susan Zhang, ^{sa}, Kenneth E. Towbin, ^{no}, Melissa A. Brotman, ^{no}, Daniel S. Pine, ^{no}, Ellen Leibenluft, ^{no}

The present study is the first to compare neural and behavioral alterations in attentional functioning in ADHD and DMDD, with evidence of specific and shared dysfunctions. Specifically, when quantifying precisely trial-wise associations between RT and BOLD activity, we identified increases in pre-stimulus activity associated with long RT trials in youth with DMDD compared with youth with ADHD and HVs. However, in patients with ADHD and those with DMDD compared with HVs, we identified blunting of the peak activation in trials with long RTs. This peak could represent compensatory activity that occurred in response to the long RT trials in healthy youth but failed to manifest in those with ADHD or DMDD. In an exploratory follow-up, this blunting was related to an increased EVRT across the sample in most identified regions. When examining average BOLD activity, as in typical fMRI analyses, we identified increases in activity specific to DMDD during this attentional paradigm.

J Am Acad Child Adolesc Psychiatry 2017;56(5):426–435.

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Brain Mechanisms of Attention Orienting Following Frustration: Associations With Irritability and Age in Youths

Wen-Ling Tseng, Ph.D., Christen M. Deveney, Ph.D., Joel Stoddard, M.D., Katharina Kircanski, Ph.D., Anna E. Frackman, M.D., Jennifer Y. Yi, M.A., Derek Hsu, M.D., Elizabeth Moroney, B.A., Laura Machlin, B.A., Laura Donahue, B.A., Alexandra Roule, B.A., Gretchen Perhamus, B.A., Richard C. Reynolds, M.S., Roxann Roberson-Nay, Ph.D., John M. Hettema, M.D., Ph.D., Kenneth E. Towbin, M.D., Argyris Stringaris, M.D., Ph.D., Daniel S. Pine, M.D., Melissa A. Brotman, Ph.D., Ellen Leibenluft, M.D.

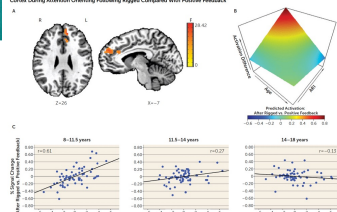
Results: Whole-brain activation analyses revealed associations with irritability during attention orienting following frustration. Irritability was positively associated with frontal-striatal activation, specifically in the dorsolateral prefrontal cortex, inferior frontal gyrus, and caudate. Age moderated the association between irritability and activation in some frontal and

tration. Irritability was positively associated with frontal-striatal activation, specifically in the dorsolateral prefrontal cortex, inferior frontal gyrus, and caudate. Age moderated the association between irritability and activation in some frontal and posterior regions (the anterior cingulate cortex, medial frontal gyrus, cuneus, precuneus, and superior parietal lobule [$F=$

ry 2019

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FIGURE 2. Age Moderating the Association Between Irritability and Activation in the Neural Prefrontal Cortex and Anterior Cingulate Cortex During Attention Orienting Following Frustration Compared With Positive Feedback



Conclusions: Following frustration, levels of irritability correlated with activity in neural systems mediating attention orienting, top-down regulation of emotions, and motor execution. Although most associations were independent of age, dysfunction in the anterior cingulate cortex and posterior regions was more pronounced in young children with irritability.

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White Matter Microstructure in Pediatric Bipolar Disorder and Disruptive Mood Dysregulation Disorder

Julia O. Linke, PhD, Nancy E. Adelman, PhD, Joelle Sarlis, PhD, Andrew Ross, BA, Samantha Perlstein, BA, Heather R. Frank, BA, Kenneth E. Towbin, MD, Daniel S. Pine, MD, Ellen Leibenluft, MD, Melissa A. Brotman, PhD

Dr. Linke and Adelman contributed equally to this work.

Objective: Disruptive mood dysregulation disorder (DMDD) codifies severe, chronic irritability. Youths with bipolar disorder (BD) also present with irritability, but with an episodic course. To date, it is not clear whether aberrant white matter microstructure—a well-replicated finding in BD—can be observed in DMDD and relate to symptoms of irritability.

Method: We acquired diffusion tensor imaging data from 118 participants (BD = 36, DMDD = 44, healthy volunteers (HV) = 38). Images of fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were processed with tract-based spatial statistics controlling for age and sex. The data were also used to train Gaussian process classifiers to predict diagnostic group.

Results: In BD vs DMDD, FA in the corticospinal tract was reduced. In DMDD vs HV, reductions in FA and AD were confined to the anterior corpus callosum. In BD vs HV, widespread reductions in FA and increased RD were observed. FA in the anterior corpus callosum and corticospinal tract was negatively associated with irritability. The Gaussian process classifier could not discriminate between BD and DMDD, but achieved 68% accuracy in predicting DMDD vs HV and 75% accuracy in predicting BD vs HV.

Conclusion: Aberrant white matter microstructure was associated with both categorical diagnosis and the dimension of irritability. Alterations in DMDD were regionally discrete and related to reduced AD. In BD, we observed widespread increases in RD, supporting the hypothesis of altered myelination in BD. These findings will contribute to the neurobiological understanding of DMDD and its differentiation from BD.

Conclusion: Aberrant white matter microstructure was associated with both categorical diagnosis and the dimension of irritability. Alterations in DMDD were regionally discrete and related to reduced AD. In BD, we observed widespread increases in RD, supporting the hypothesis of altered myelination in BD. These findings will contribute to the pathophysiological understanding of DMDD and its differentiation from BD.

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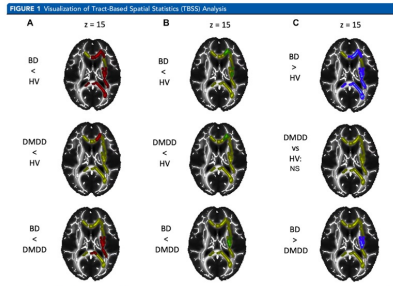


FIGURE 1. Visualization of Tract-Based Spatial Statistics (TBSS) Analysis. A: BD vs HV. B: DMDD vs HV. C: BD vs DMDD. Red-colored voxels indicate significant decreases in fractional anisotropy (FA) ($p < 0.05$). Green-colored voxels indicate significant increases in FA ($p < 0.05$). Blue-colored voxels indicate non-significant results. The maps show the brain's white matter tracts with color-coded regions of interest.

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In additional analyses to parse the three subgroups using the white matter microstructural differences, Linke *et al.* trained a Gaussian process classifier (GPC) to estimate the likelihood that an individual would belong to one of the three subgroups. Having an algorithm that can estimate specific diagnoses based on the underlying neurobiology may prove beneficial for early diagnosis and personalized treatment in

the future. The current algorithm was able to discriminate between DMDD vs controls and between BPAD vs controls, but not between DMDD vs BPAD. Moreover, the accuracy for BPAD was 75%, whereas for DMDD it was only 68%, implying that far too many participants would be misclassified in a clinical setting. Furthermore, it is also unclear

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Assessment of DMDD

- There is no consensus or even well-validated scales for the assessment of DMDD nor gold standard measures for the assessment of irritability in children.
- Most parent and teacher rating scales measuring irritability and tantrums focus on the frequency of such events, with less emphasis on duration or severity.
- Few measures capture qualitative descriptions of temper outbursts that provide detailed descriptions of the triggers, duration, and intensity of temper outbursts that would be helpful for diagnosing DMDD in children with other oppositional behaviors.



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Assessment of DMDD (cont.)

- There are several established measures for assessing aggressive behaviors, but physical aggression is not a requirement for DMDD, as temper outbursts can be verbal and many aggressive youth do not exhibit persistent irritability.
- Therefore, ratings scales measuring aggression may not be the best assessment tools for DMDD.
- A sizable percentage of children with temper outbursts and frequent irritable mood will not meet the other criteria for DMDD.
- Therefore, it is important to assess all the inclusion and exclusion criteria. In addition, parents may interpret the term "temper outbursts" differently based on the frequency of their child's disruptive behaviors, so it is important to query parents about details of their child's reaction to frustration or other negative stimuli.
- As irritability is associated with a wide range of disorders and is a common reaction to negative life events in children, it is important to explore all the potential causes of chronic irritability rather than ending the inquiry once a diagnosis of DMDD is reached.

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Assessment of DMDD (cont.)

- This includes examination for conflicts within the family, at school, or in other settings, as well as for evidence of past trauma and a wide range of psychiatric disorders.
- Meeting the criteria for DMDD should not stop the search for triggers for the child's irritability, as this diagnosis does not require an identified etiology for the child's distress.
- Any efficacious psychosocial treatment for DMDD will likely necessitate some degree of antecedent management, making it even more important to identify environmental stressors.
- This approach is more likely to facilitate a treatment plan incorporating psychosocial interventions, liaison with the child's school, and involvement in all available community resources to treat the actual functional impairments versus sole reliance on medication, in an attempt to reduce irritability or aggression.

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Assessment of DMDD (cont.)

- Start with a broad-spectrum questionnaire for parents and teacher given high rates of comorbidity in DMDD.
- Give narrow-spectrum questionnaires if indicated for autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, or depression.
- Include a risk/resilience measure with latency and teenage youth such as the Risk Inventory and Strengths Evaluation: <https://www.wopublish.com/rise-assessment-risk-inventory-and-strengths-evaluation>.
- Consider developmental assessment if indicated, including language, intellect, neuropsychological, executive function, and achievement.
- Clinical Comorbidity and IDEIA Eligibility is likely the rule rather than the exception.

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Disruptive Mood Questionnaire (DMQ)

5. act afraid when away from parents.

How often: ☐ Never ☐ Very Rarely ☐ Rarely ☐ Occasionally ☒ Frequently ☐ Very Frequently

How intense: ☐ Not much at all ☐ Slightly ☐ Mildly ☒ Moderately ☐ Very ☐ Extremely

How long: ☐ Under 10 min ☐ Under 30 min ☐ Under 1 hr ☐ Under 2 hrs ☒ More than 2 hrs ☐ Almost all day

6. have temper outbursts.

How often: ☐ Never ☐ Very Rarely ☐ Rarely ☐ Occasionally ☒ Frequently ☐ Very Frequently

How intense: ☐ Not much at all ☐ Slightly ☐ Mildly ☐ Moderately ☒ Very ☐ Extremely

How long: ☐ Under 10 min ☐ Under 30 min ☐ Under 1 hr ☐ Under 2 hrs ☒ More than 2 hrs ☐ Almost all day

7. act based on emotion.

How often: ☐ Never ☐ Very Rarely ☐ Rarely ☐ Occasionally ☒ Frequently ☐ Very Frequently

How intense: ☐ Not much at all ☐ Slightly ☐ Mildly ☐ Moderately ☒ Very ☐ Extremely

How long: ☐ Under 10 min ☐ Under 30 min ☐ Under 1 hr ☐ Under 2 hrs ☒ More than 2 hrs ☐ Almost all day

8. get rejected by peers.

How often: ☐ Never ☐ Very Rarely ☐ Rarely ☐ Occasionally ☒ Frequently ☐ Very Frequently

How intense: ☐ Not much at all ☐ Slightly ☐ Mildly ☐ Moderately ☒ Very ☐ Extremely

How long: ☐ Under 10 min ☐ Under 30 min ☐ Under 1 hr ☐ Under 2 hrs ☒ More than 2 hrs ☐ Almost all day

To be published worldwide in 2024 by Guinti Psychometrics.

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DMQ Structure

DMDD Total Scale	Symptom Scales
Frequency Scale	Irritability
Duration Scale	Mood Fluctuations
Intensity Scale	Aggression
	Anger Expression
DSM 5 DMDD Total Scale	Impulsivity
DSM 5 Outburst Scale	Hyperactivity
DSM 5 Irritability Scale	Socialization

Mean = 50; S.D. = 10, high scores problematic.

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DMDD and Special Education

- The USA Individuals with Disabilities Education Act (IDEA) requires public schools to provide special education and related services to eligible students, but not every child who struggles in school qualifies. To be covered, a child's school performance must be "adversely affected" by a disability in one of the 13 categories.
- **Other Health Impairment.** The "other health impairment" category covers conditions that limit a child's strength, energy, or alertness. One example is **ADHD**, which impacts attention and executive function.
- **Emotional Disturbance.** Various mental health issues can fall under the "emotional disturbance" category. They may include anxiety disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder, and depression. DMDD?
- **Multiple Disabilities.** A child with multiple disabilities has more than one condition covered by IDEA. Having multiple issues creates educational needs that can't be met in a program designed for any one disability.

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- *Difficult Students and Disruptive Behavior in the Classroom: Teacher Responses That Work*, by Vance Austin, PhD, and Daniel Sciarra, PhD.
- *Learning Disabilities and Challenging Behaviors: Using the Building Blocks Model to Guide Intervention and Classroom Management* (3rd ed.), by Nancy Mather, PhD, Sam Goldstein, PhD, and Katie Eklund, PhD.

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Psychiatric Treatment of DMDD

- Limited formal treatment studies of youth with DMDD have been conducted.
- There is an expanding database for SMD and related conditions (e.g., ADHD plus aggression, ADHD, and ODD). While SMD is the most similar diagnostic construct to DMDD, it is important to emphasize that it is not presently clear how well treatment effects for SMD translate to DMDD.
- Behavioral and medication treatments targeting ADHD symptoms in the Multimodal Treatment Study of Children with ADHD were associated with reduced levels of irritability in children with ADHD.



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Psychiatric Treatment of DMDD (cont.)

- The only randomized, placebo-controlled trial of medication in children with SMD found no benefit of lithium over placebo. However, others have examined medication effects in related phenotypes.
- A controlled trial in youth ($N = 27$) with ADHD and aggressive behavior refractory to stimulant monotherapy (a phenotype similar to SMD) found Depakote (an anticonvulsant) combined with CNS stimulants and behavioral therapy to be more effective than placebo combined with a CNS stimulant and behavioral therapy.
- In both these studies, all participants also received psychosocial treatments prior to the randomization. In the Blader et. al. study, CNS stimulant dose was optimized prior to assignment to Depakote or placebo. Approximately half of the samples in each study improved to the degree that they no longer met the entry criteria.
- Oxcarbazepine (an anticonvulsant) in combination with amantadine (an antidyskinetic) has been proposed. The first medication to enhance frontal lobe function (top-down) to control irritability, and the second to stabilize temporal-limbic (bottom-up) to stop explosive outbursts.
- [Qxylocin?](#)

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A Proposed Comprehensive Psychosocial Intervention for Children Diagnosed With Disruptive Mood Dysregulation Disorder

Thomas A. Smith, MA

This [manual](#), completed as part of a 2018 dissertation, outlines an 8-session program for children and parents to learn the practical application of behavioral principles in behavior modification, coping skills, emotion awareness, and self-regulation skills. Weekly data collection is built into the protocol to facilitate progress monitoring as well as overall efficacy of the manual.

- Emotion Regulation
- Psychoeducation
- Tantrum Management and Successive Approximation
- Behavioral Activation
- Mindfulness
- Irritability
- Emotional Identification in Others
- Termination

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Psychosocial Treatment of DMDD: References

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Should We Consider CAM Treatments?

- [The Marshall Protocol](#): Dr. Marshall suggests that autoimmune diseases are due to a correctable defect in innate immunity from a dysregulation of vitamin D. This immunologic defect allows L-form (cell wall-deficient) bacteria, to proliferate.
- [Brain Training?](#)
- Chiropractic Manipulation
- Homeopathy
- Acupuncture
- Aromatherapy
- Related [literature review](#)

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Support for Parents



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Conclusions

- There are a group of children experiencing severe mood dysregulation and intermittent irritability.
- The DSM 5 criteria provide a basic framework for diagnosis.
- However large scale epidemiologic studies still need to be undertaken.
- A large group of referred children frequently demonstrate some symptoms of DMDD.
- Children with DMDD have a high rate of comorbidity.
- DMDD is a distinct condition, with chronic (non-episodic) irritability, that does not evolve into BD.
- No well established treatment strategies for DMDD.

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Conclusions *(cont.)*


- As of this date there is not a norm referenced behavioral tool to specifically identify children with symptoms of DMDD.
- These children often end up with a combination of psychiatric medications with a less than optimal response.
- This severe mood disorder appears to be relatively common (DMDD at least 3%, versus 1% for BD)
- No established treatment strategies for DMDD.
- IDEIA does not include DMDD as an identified disorder.

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Conclusions *(cont.)*

- Currently the best approach to treat DMDD consists of:
 1. Medications (Many children end up on a combination often after lots of trials).
 2. Parent Training and [ongoing support](#). Likely ABA strategies in home will help. Also consider Ross Greene's approach.
 3. Cognitive Behavioral Therapy focused on support and specific challenges as they arise.
 4. Modified crisis management strategies.
 5. IDEIA or ADA 504 support most likely under ED eligibility.
 6. Reasonable consideration of CAM treatments.

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TEDx


Sam Goldstein, Ph.D.
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The Power Of Resilience

https://www.youtube.com/watch?v=stHfUJ-4fW6k8tuturn-youtube_gdota

Would you like to be part of my data collection or contribute to my DMDD textbook?

THANK YOU



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