Neural Mechanisms in Chronic Irritability

In a clinical trial, children with chronic irritability showed marked deactivation of neural regions associated with spatial attention, reward processing, and emotional salience during a frustrating game task. The results suggest frustration may impair attention flexibility.

Methods: Study participants were 19 young patients, aged 8–17 years, with severe mood dysregulation, all of whom would have met DSM-5 criteria for disruptive mood dysregulation disorder. All patients lacked symptoms of mania or hypomania that would qualify them for a diagnosis of bipolar disorder. Also included was a comparison group of 23 healthy children and adolescents with no current or past psychiatric illness. All participants played an experimental video game for monetary rewards based on the speed and accuracy of response. After learning the game, they played while anatomic brain images were obtained. Frustration was induced by telling the children that they were responding too slowly.

Results: Participants were an average age of about 14 years. Seven of the children with irritability were unmedicated, and the rest were receiving multiple medications. All had multiple comorbid diagnoses, the most common being ADHD, anxiety, and oppositional defiant disorder. Both the children with chronic irritability and the control group had decreased ability to shift spatial attention during the frustration condition compared with the non-frustration condition, but the decrease was greater in the children with chronic irritability.

In response to the trials in which they were told they were too slow, children with chronic irritability showed less activation of the left amygdala (p<0.04) and left and right striatum (p<0.03), compared with healthy controls. Children with severe mood dysregulation also had reduced activity in the parietal, parahippocampal, and thalamic/cingulate/striatal regions during frustration trials, compared with controls (p<0.005 for all). Hypoactivation of these regions may be associated with flexibility in diverting attention from a blocked goal to more positive stimuli or difficulty employing emotional regulation strategies. Brain activity did not differ between the 2 groups during trials in which the child received positive feedback. Results were similar in medicated and unmedicated children with mood dysregulation.
Editorial: Clinicians are often faced with the difficulty of patients who are impaired but do not exactly fit the criteria for the disorder they seem to have. Children like the ones studied are often presumed to have a bipolar-like disorder, which is typically treated with atypical antipsychotics. The new DSM-5 diagnosis of disruptive mood dysregulation disorder, while controversial, has the virtue of separating out a group of children with a low likelihood of developing bipolar disorder. The frustration experiment represents a new research approach that may help clarify matters by starting with an important symptom that can be measured dimensionally and spans multiple disorders, and then investigating disruptions of the underlying neural systems.


Substance Use Disorders and Bipolar Disorder

Bipolar disorder in adolescents is known to be associated with a high incidence of substance use disorders (SUDs). A longitudinal study identified factors predictive of greater risk and suggested that there is a long window of opportunity for intervention between the onset of bipolar disorder and substance abuse problems.

Methods: Study participants were enrolled in the ongoing Course and Outcome of Bipolar Youth (COBY) study. The present sample comprised 167 adolescents, aged 12–17 years, who were free of substance use disorders at intake. Participants were interviewed an average of 7 times over about 4 years. Substance use disorders were identified using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version. Nicotine dependence was not included among the disorders.

Results: Substance use disorders developed in 54 adolescents (32%) during follow-up. The mean age at onset was 18 years, and the disorders occurred after an average of 2.7 years of follow-up. Cannabis and alcohol abuse or dependence accounted for nearly all SUDs. Three-fourths of these patients had problems with both cannabis and alcohol.

Of the study participants, 65% had bipolar I disorder, 12% had bipolar II disorder, and 23% had bipolar disorder not otherwise specified. Risk of an SUD was similar for the 3 bipolar subtypes. The subjects were more likely to progress to a substance use disorder if they had reported cigarette smoking or any use of marijuana or alcohol at study entry (p<0.05 for each of these exposures). Substance use disorders were also associated with a lifetime history of oppositional defiant disorder (ODD); lifetime panic disorder; family history of SUD; increased negative life events; low family cohesion; and a lack of treatment with antidepressants. (See table.) Youths with a higher number of these predictors at study intake were at increasing risk of substance abuse; the incidence was 14% in adolescents with ≤2 predictors, 46% in those with 3 predictors, and 75% in those with 4 or 5 (p<0.0001). Use of lithium was associated with reduced risk of substance abuse.

<table>
<thead>
<tr>
<th>Predictors of SUD Onset in Youths with Bipolar Disorder</th>
<th>Risk Factor</th>
<th>Hazard Ratio*</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime alcohol use</td>
<td>4.33</td>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>Lifetime panic disorder</td>
<td>2.74</td>
<td>p=0.02</td>
<td></td>
</tr>
<tr>
<td>Lifetime ODD</td>
<td>2.33</td>
<td>p=0.01</td>
<td></td>
</tr>
<tr>
<td>Family history of SUD</td>
<td>2.54</td>
<td>p=0.008</td>
<td></td>
</tr>
<tr>
<td>Low family cohesiveness</td>
<td>2.04</td>
<td>p=0.04</td>
<td></td>
</tr>
<tr>
<td>No antidepressant use</td>
<td>2.23</td>
<td>p=0.04</td>
<td></td>
</tr>
</tbody>
</table>
**Discussion:** Findings in the total COBY cohort indicate that half of all adolescents with bipolar disorder will experience full-threshold SUDs by early adulthood. The authors predict that another 10–20% of the cohort will develop substance use disorders as they age. The strong association of experimentation with substances and development of SUDs suggests that deferring the initiation of substance use may help prevent full-blown disorders.

Goldstein B, Strober M, Axelson D, Goldstein T, et al: Predictors of first-onset substance use disorders during the prospective course of bipolar spectrum disorders in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 2013;52 (October):1026–1037. From the University of Pittsburgh School of Medicine, PA; and other institutions. Funded by the NIMH; and the Sunnybrook Foundation. Several study authors disclosed financial relationships with commercial sources.

*See Reference Guide.

### Effects of Maternal Depression: Timing and Mechanisms

According to results of a large cohort study, maternal pre- and postnatal depression appear to be independent risk factors for offspring depression in late adolescence, possibly acting via different mechanisms.

**Methods:** All pregnant women living in southwest England with an estimated date of delivery in 1991–1992 were invited to take part in the longitudinal study. Maternal depression and its correlates were assessed in nearly 9000 pregnancies. The final sample consisted of nearly 3000 adolescents from singleton pregnancies in which complete data were available for: maternal prenatal and postnatal depression; offspring outcomes at age 18 years; and possible confounding variables. Information on paternal depression and education was available for about 85% of the final sample. Depression was measured using the Edinburgh Postnatal Depression Scale (EPDS), which has been validated in nonpregnant women and in men. Maternal depression was assessed at 18 and 32 weeks of gestation and at 8 weeks and 8 months postnatally. Fathers also completed the EPDS at 18 weeks of gestation and 8 months postnatally. Adolescent depression was measured with the Clinical Interview Schedule–Revised.

**Results:** Nearly 12% of women experienced depression during pregnancy, and 7% postnatally. Pre- and postnatal depression were highly correlated (correlation coefficients,* 0.6–0.7). A total of 8% of the offspring met criteria for depression at age 18 years. Adolescent depression was significantly associated with both prenatal depression (odds ratio [OR],* 1.47; p=0.047) and postnatal depression (OR, 1.67; p=0.03). The association between prenatal and offspring depression remained significant when postnatal depression was included in the statistical model, but not vice versa. The effect of postnatal depression was limited to mothers with lower education, but prenatal depression was associated with risk regardless of maternal education. Postnatal depression in the father was associated with offspring depression, but only for fathers with low education.

**Discussion:** These findings suggest some hypotheses about the mechanisms of transmission of depression across generations. Prenatal depression is an independent risk factor, but postnatal parental depression appears to confer risk only in disadvantaged families. Maternal prenatal depression does not appear to operate simply by continuing into the postnatal period, but instead has a separate pathway involving the biological consequences of depression in utero. This possibility is supported by the absence of an effect of paternal prenatal depression. The moderating effect of parental education on postnatal depression indicates a pathway involving the environment, such as greater use of prenatal care and a positive home environment.

Pearson R, Evans J, Kounali D, Lewis G, et al: Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* 2013; doi 10.1001/jamapsychiatry.2013.2163. From the University of Bristol, UK; and other institutions. Funded by the Wellcome Trust; and other sources. The study authors declared no conflicts of interest.

*See Reference Guide.
ADHD and Constipation/Incontinence

Children with ADHD had 3–6 times the rate of constipation or fecal incontinence as their peers in a large claims-based study. The prevalence of defecation disorders was not related to use of ADHD medication.

**Background:** Functional constipation, the most common form in childhood, often coexists with fecal incontinence. Causes include a diet low in fiber and behavioral withholding of stool. A few studies have observed associations of functional constipation with emotional or behavioral symptoms in children, but the present study appears to be the first in children with a diagnosis of ADHD. Possible explanations for the association, which are supported by preliminary data, include a common underlying neurobiological disorder and altered communication between the central and enteric nervous systems. Deficits in attention, poor motivation for toilet training, and nutritional deficiencies are among the other potential contributors.

**Methods:** A retrospective cohort study was performed using the health care delivery database for all U.S. uniformed military personnel and their families. The analysis included nearly 750,000 children who were between ages of 4 and 12 years in 2005–2007. The presence of ADHD, constipation, and fecal incontinence were ascertained from diagnostic codes. Medication use for ADHD was also evaluated.

**Results:** In the study cohort, 32,773 children (4.4%) had a diagnosis of ADHD; 80% of those children were receiving medication. Nearly 13,000 children (1.7%) saw a clinician for either constipation or fecal incontinence. Some 4.1% of children with ADHD, compared with 1.5% of children without ADHD, saw a provider for constipation (relative risk,* 2.88; p<0.001). Children with ADHD also had a higher rate of diagnosed fecal incontinence: 0.9% vs. 0.15% of children without ADHD (relative risk, 6.19; p<0.001). Rates of medical visits for these disorders and prevalences adjusted for demographic factors differed by a similar proportion between children with and without ADHD. Among children with ADHD, rates of constipation, incontinence, and visits for constipation or fecal incontinence did not differ from those in children who were unmedicated.

McKeown C, Hisle-Gorman E, Eide M, Gorman G, et al: Association of constipation and fecal incontinence with attention-deficit/hyperactivity disorder. *Pediatrics* 2013;132 (November):e2010–e2015. From the Uniformed Services University of the Health Sciences, Bethesda, MD. This study was conducted without external funding. The authors declared no conflicts of interest.

*See Reference Guide.

ADHD Drugs and Growth

According to results of a cohort study, both atomoxetine and methylphenidate are associated with modestly slowed growth over 2 years. The reduction in height gains appears to be transient. Children gained weight during treatment, leading to concerns about obesity risk, but treatment was also associated with a relative slowing in weight gain.

**Methods:** Study subjects were enrolled in the Italian ADHD National Registry, a mandatory registry for all patients receiving ADHD medications. Patients are required to undergo 2 years of close monitoring after registration. The study cohort included children and adolescents, aged 6–18 years, with a diagnosis of ADHD (DSM-IV) and who were receiving treatment with either atomoxetine or methylphenidate according to clinical judgement. Height and weight were measured monthly. Results were analyzed from baseline to 6, 12, and 24 months.

**Results:** Of an initial cohort of 1758 patients, two-thirds were excluded because they had only 1 follow-up evaluation; were followed for <6 months; had insufficient data on weight, height, or drug therapy; or were treated with both drugs. The final cohort consisted of 590...
patients with available weight measurements and 574 with height measurements. More than half of the patients (58%) were aged <11 years, 35% were aged 11–14 years, and 7% were ≥15 years. About half of patients (n=296 for methylphenidate; n=294 for atomoxetine) were treated with 1 of the 2 drugs.

In both groups, patients gained weight, but most patients shifted to a lower weight percentile after 6, 12, and 24 months. The shift was larger in patients who received atomoxetine than methylphenidate. From baseline to 24 months, the proportion of patients shifting to a lower weight percentile was 42% for methylphenidate and 54% for atomoxetine; 27% and 14%, respectively, were in a higher weight percentile than at baseline.

The proportion of patients shifting to a lower percentile of height was also greater than the proportion shifting to a higher percentile. The difference from baseline was statistically significant only for atomoxetine and only at some time points. In comparisons using the z score, which correlates with chronological age and gender, height in patients taking methylphenidate differed significantly from population norms only at 12 months (p<0.001), and height in those taking atomoxetine differed from norms at 12 and 24 months (p≤0.001 for both). With regard to height, atomoxetine differed statistically from methylphenidate only at 1 year (p=0.006).

**Discussion:** The authors conclude that patients who took atomoxetine grew significantly more slowly than those treated with methylphenidate. It is not clear whether the observed slowdown in growth is transient or whether there is rebound growth after drug discontinuation. The 2-year data indicate the effects may not be permanent. The authors suggest that weight should be followed as closely as height in children taking ADHD medications.


From Istituto Superiore di Sanità, Rome, Italy; and other institutions. Funded by the Italian Medicine Agency. The authors declared no conflicts of interest.

**Drug Trade Names:** atomoxetine—Strattera; methylphenidate—Ritalin

---

**Emotional Control Deficits in ADHD**

Results of a post-hoc analysis of an open-label trial of lisdexamfetamine dimesylate (*Vyvanse*) found that emotional control dysfunction is common in children with ADHD. The high rates of dysfunction suggest that emotional status should be assessed in patients with ADHD. Lisdexamfetamine treatment appears to improve these emotion control deficits.

**Methods:** Participants in this 7-week lisdexamfetamine dose-optimization study were children, aged 6–12 years, with a primary diagnosis of ADHD, age appropriate intellectual functioning, and no comorbid conduct disorder. Emotional function was primarily measured with the emotional control subscale of the parent-rated Behavior Rating Inventory of Executive Function (BRIEF). This 10-item subscale measures executive function control over behaviors reflecting emotional response, such as anger or tearfulness. The BRIEF uses T-scores, such that a score of 50 represents the normative population mean and a score that is ≥1.5 standard deviation higher represents impairment. A second measure of emotional function was the parent-reported Expression and Emotion Scale for Children (EESC), which measures positive and negative aspects of emotional expression.

**Results:** A total of 315 study participants were characterized at baseline: 53% had impairments in BRIEF emotional control and 47% did not. The group with impaired emotional control at baseline had a greater improvement in this subscale during treatment than the group without impairment, so that both groups had similar outcomes. At study end, only 21% of children met criteria for emotional impairment. When emotional control was measured with the EESC, results both at baseline and after treatment were similar to the BRIEF results.
Discussion: Previous research results suggest ADHD core symptoms are more pronounced with increasing severity of emotional lability. However, psychostimulants reportedly can both improve and worsen emotional symptoms in children with ADHD. Results from the present study suggest that lisdexamfetamine may improve these symptoms in some patients and underscores the importance of evaluating emotional control in addition to core symptoms of ADHD.

Katic A, Dirks B, Babcock T, Scheckner B, et al: Treatment outcomes with lisdexamfetamine dimesylate in children who have attention-deficit/hyperactivity disorder with emotional control impairments. Journal of Child and Adolescent Psychopharmacology 2013;23 (August):386–393. From private practice, Houston, TX; Shire Development, LLC, Wayne, PA; and Johns Hopkins University, Baltimore, MD. Funded by Shire Development, LLC. All study authors disclosed financial relationships with commercial sources including Shire, the manufacturer of Vyvanse.

Reference Guide

Correlation Coefficient: A measure of the closeness of the relationship between two variables. The value can range from -1 to 1. A value near 1 indicated a strong positive relationship. A value close to zero indicates no relationship, and a negative value indicates a negative relationship.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION


Contributing Editors: Kate Casano, MSHyg  Bennett Silver, MD
Consulting Editor: Theodore A. Petti, MD, UMDNJ–Robert Wood Johnson Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Krista Strobel
Founding Editor: Michael J. Powers

Off-Label Drug Use Statement: Some drugs discussed for specific indications in Child & Adolescent Psychiatry Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.