MRI Studies Suggest Dimensional View of ADHD

Cortical growth reaches a peak in early childhood, before giving way to a phase of cortical thinning that lasts throughout late childhood and early adolescence. Research has shown that the peak is delayed in children with ADHD, who also show a slower rate of subsequent cortical thinning. A longitudinal study now shows that slowing of cortical thinning also occurs in children with subthreshold symptoms of hyperactivity and impulsivity, supporting the idea that ADHD is a dimensional disorder rather than one with clear diagnostic boundaries.

Methods: Study subjects were 193 typically developing children with no history of psychiatric or neurological disorders and 197 children with ADHD. Normally developing participants underwent a structured interview to rule out psychiatric diagnoses, and those who became mentally ill during the study were excluded. Each child underwent at least 2 neuroanatomic MRI scans between the ages of 8 and 18 years. Hyperactive and impulsive symptoms were measured with a version of the Conners’ Rating Scale. The typically developing children were divided into an asymptomatic group and 2 groups with minimal or moderate hyperactive/impulsive symptoms. All of the children with ADHD had symptom scores higher than the children without a diagnosis. The investigators examined whether the rate of cortical thinning was affected by the severity of hyperactive/impulsive symptoms.

Results: The rate of cortical thinning over time varied substantially and was associated with hyperactive/impulsive symptom scores. The rate was slowest in children with ADHD and increased progressively in each group as symptom severity decreased. The differences were most pronounced in multiple regions of the right and left prefrontal cortex and less marked in the posterior cortex.

Severity of conduct symptoms was also examined as a measure of the specificity of the effect of reduced cortical thinning. The cortical regions that varied significantly with the conduct problem score were relatively few and concentrated in regions that overlapped only partially with those involved in ADHD.

Discussion: These findings suggest that a disturbance of the cortical growth trajectory is a fundamental deficit in the pathogenesis of ADHD. Affected regions are associated with...
cognitive functions that are impaired in ADHD: the ability to inhibit responses to achieve later goals and the processing of reward and punishment.

Shaw P, Gilliam M, Liverpool M, Weddle C, et al: Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention-deficit/hyperactivity disorder. *American Journal of Psychiatry* 2010; doi 10.1176/appi.ajp.2010.10030385. From the NIMH; and McGill University, Montreal, Que., Canada. **Funded by the NIMH. The authors reported no competing interests.**

### Amantadine for ADHD

In a controlled trial, amantadine significantly reduced symptoms of ADHD. Efficacy did not differ significantly from methylphenidate.

**Methods:** Study participants were 40 patients, aged 6–14 years (mean age, 9 years; 28 males), with newly diagnosed combined-type ADHD. Patients with other Axis I disorders were excluded, as were those receiving psychopharmacological treatment or with blood pressure concerns. Following clinical assessment, participants were randomized to double-blind treatment with either amantadine or methylphenidate for 6 weeks. Amantadine was titrated in 50-mg increments to 100 mg/day for patients weighing less than 66 lbs and to 150 mg/day for heavier patients. Methylphenidate was titrated in 10-mg increments to 20 or 30 mg/day, depending on weight. Outcomes were assessed at 4 and 6 weeks using the Parent and Teacher versions of the ADHD Rating Scale-IV (ADHD-RS-IV). Response was defined as a ≥50% decrease in ADHD-RS-IV score.

**Results:** Mean baseline parent-rated total ADHD-RS-IV scores were 32 and 33 points in the amantadine and methylphenidate groups, respectively. Teacher-rated scores were 24 and 25, respectively. Patients in both treatment groups improved significantly. On the parent rating scale, statistically significant improvement from baseline was evident at 4 and 6 weeks; final scores improved by 14 points with amantadine and by 16 points with methylphenidate. Response rates for the 2 drugs were 50% and 55%, respectively. On the teacher rating scale, improvement was also statistically significant at both evaluation times; scores improved by 5 points with amantadine and by 9 with methylphenidate. Response was evident in 30% and 35% of patients, respectively.

One patient in each treatment group withdrew from the study, both for lack of parent collaboration. Mild-to-moderate adverse effects, including sleep disturbance, nausea, dry mouth, nervousness, and headache, were common but tolerable and comparable in frequency with the 2 drugs. Decreased appetite and restlessness occurred significantly less often in patients taking amantadine.

**Discussion:** Amantadine is a dopamine antagonist used to treat Parkinson’s disease and drug-induced parkinsonism. Experience with the drug in ADHD is extremely limited. A few preliminary reports have suggested it is well tolerated, but less effective than methylphenidate. Although the results of the present study should also be considered preliminary, they suggest amantadine may be an effective option for patients who do not respond to or are unable to tolerate stimulants.

**Study Rating**—17 (100%): This study met all criteria for a randomized clinical trial; however, the lack of a placebo-control group is an important limitation.

Mohammadi M, Kazemi M, Zia E, Rezazadeh S, et al: Amantadine versus methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder: a randomized, double-blind trial. *Human Psychopharmacology: Clinical and Experimental* 2010; doi 1010.1002/hup.1154. From Tehran University of Medical Sciences, Tehran, Iran. **Funded by Tehran University of Medical Sciences. The authors did not include disclosure of competing interests.**

**Drug Trade Names:** amantadine—*Symadine, Symmetrel*; methylphenidate—*Ritalin*

*See Reference Guide.
Engaging parents in a brief group intervention appears to have a protective effect in young children at risk of anxiety disorders.1

**Methods:** Children, aged 3–5 years, who were at risk for anxiety were identified using a screening questionnaire distributed mainly in preschools. To enter the study, children were required to show behavioral inhibition in multiple situations in a laboratory evaluation. A total of 146 qualifying families were randomly assigned to the active parent intervention or to an observation group. Treatment consisted of six 90-minute group sessions, attended by about 6 parents or sets of parents. Sessions covered education and motivation; management techniques, including avoidance of overprotection; application of exposure; and cognitive restructuring. Initial results of this study, reported previously, showed a small reduction in anxiety disorders in the children whose parents received the intervention.2 The present report describes the results of longitudinal follow-up at 2 and 3 years.

**Results:** At study entry, children had an average of about 2 anxiety disorder diagnoses, the most frequent being social phobia (82%), specific phobias (54%), and separation anxiety disorder (38%). Follow-up comparisons showed significantly fewer diagnoses in the children receiving the active treatment at 2 and 3 years. By year 3, the mean number of diagnoses was 0.57 in the treated group and 1 in controls. The clinical severity of anxiety symptoms was also significantly lower in the treated children at 2 and 3 years. (See table.) Parent reports and lab ratings of inhibition decreased with time but did not differ between treatment groups.

<table>
<thead>
<tr>
<th>Number of Anxiety Diagnoses</th>
<th>Severity of Anxiety Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Intervention</td>
<td>2.06</td>
</tr>
<tr>
<td>Comparison</td>
<td>1.84</td>
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</tbody>
</table>

**Discussion:** It has been suggested that an inhibited temperament in early childhood increases later risk for anxiety disorders, depression, and other internalizing problems. It is interesting that the study intervention did not act via reducing child inhibition. The study targeted a period in childhood when anxiety disorders are common. It remains to be seen whether the protection attributed to the treatment will extend to other internalizing problems later in childhood. This type of intervention is brief and relatively inexpensive and can be applied in a variety of community settings.

1 Rapee R, Kennedy S, Ingram M, Edwards S, et al: Altering the trajectory of anxiety in at-risk young children. *American Journal of Psychiatry* 2010;167 (December):1518–1525. From Macquarie University, Sydney, Australia. **Funded by the National Health and Research Council. The authors reported no conflicts of interest.**


**Eating Disorders: Identification and Treatment**

Rates of eating disorders in children and adolescents have increased steadily over the past few decades. Although the group at greatest risk remains adolescent, caucasian girls, eating disorders are being diagnosed increasingly in boys, minority populations, and in children under 12 years. Many young patients do not fulfill strict DSM diagnostic criteria for eating disorders such as anorexia nervosa or bulimia nervosa, but have "partial syndromes" or "eating disorders not otherwise specified." These youths are nonetheless at risk for physical
and psychological complications. Eating-disorder outcomes are substantially better in young patients than in adults, and most young patients will fully recover. However, early detection and intervention are essential.

At least some of the risk for development of eating disorders appears to be genetic. Other factors may include a history of dieting behavior and neuroendocrine abnormalities. Comorbid psychiatric disorders (such as depression or anxiety) are common, particularly in patients under age 13 years, who are also less likely to binge and purge, and are more likely to be male. Young children are also less likely to meet full DSM-IV criteria for anorexia or bulimia because they do not express body image dissatisfaction or because they have growth failure rather than weight loss. Relaxation of the diagnostic criteria for eating disorders in children and adolescents has been proposed for DSM-V.

Medical stabilization and nutritional refeeding represent the core of treatment for eating disorders; these are essential before mental health interventions will succeed. Initial assessment of patients with eating disorders should include evaluation of food and weight obsessions, patient’s and parent’s understanding of diagnosis, level of treatment engagement, social functioning, and comorbid psychiatric conditions. Assessing suicidality is important as the rate of completed suicide is 25–50% higher in patients with eating disorders than in the general population. Stereotypical and obsessional eating habits are common in patients with eating disorders, and behavioral interventions are often required to encourage patients to meet necessary caloric intake and weight-gain goals.

Evidence supports family-based interventions for adolescent anorexia nervosa. These typically consist of 3 phases. In the first phase, parents ensure their adolescent is eating adequately and they limit other pathologic weight-control behaviors. In the second phase, the adolescent has attained substantial weight recovery and gradually resumes responsibility for their own eating. During the final phase, the focus of therapy shifts to address general adolescent development. Family-based treatments may not be suitable for families with parental psychopathology. Day treatment, hospitalization, or a residential setting may be required for patients with more severe or resistant symptoms. There are no medications approved for treatment of anorexia. Medication, when prescribed, is usually targeted toward comorbid depression and anxiety (SSRIs) or dysfunctional thinking (atypical antipsychotics).

Behavioral treatment of bulimia in adolescents has been poorly studied. Cognitive-behavioral therapy is the treatment of choice in adults. Fluoxetine is the only drug approved for this indication, but other SSRIs, SNRIs, and TCAs have all been shown to reduce binge eating and purging. Other options are topiramate, naltrexone, and ondansetron. Long-term prognosis is better for adolescent-onset eating disorders, but clinicians can expect to be engaged over time.


Drug Trade Names: fluoxetine—Prozac; naltrexone—ReVia; ondansetron—Zofran; topiramate—Topamax

Hormones and Aggression

Measuring hormone levels could be clinically useful in clarifying subtypes of pediatric aggression and directing patients toward subtype-specific treatments.

Pathologic aggression is a nonspecific symptom present in many disorders including ADHD, posttraumatic stress disorder, and oppositional defiant disorder. Aggression can be directed at self or others and can be either verbal or physical. Physical aggression can be further characterized as impulsive, reactive, predatory, or premeditated. Aggressive behavior in children is related to early life stress, functional and structural brain alterations, neuroendocrine abnormalities, and other biological abnormalities and social deficits.
The monoamine neurotransmitters, the hypothalamic-pituitary-adrenal (HPA) axis, and sex hormones all influence pediatric aggression in an interlinked manner. The dopaminergic system subserves emotional regulation and controls the anterior pituitary, which ultimately modulates the major hormone systems that influence aggression. Levels of dopamine are abnormal in adults with impulsive aggression, violent criminals, and youths with comorbid aggression and ADHD. Antipsychotic drugs that block central dopamine receptors have anti-aggression effects. Norepinephrine, a principal mediator of the response to stress, has a complex relationship with aggression. The serotonergic system is believed to be hypofunctional in aggressive persons, and atypical antipsychotic drugs that act on 5-HT2a receptors are often used to treat impulsive aggression.

The HPA axis has been widely studied in pediatric aggression, as it is one of the main regulators of stress in the body. The HPA axis regulates the release of cortisol from the adrenal cortex. Levels of cortisol have been low or characterized by low variability in some studies of aggressive children. In one study, children with reactive aggression had higher cortisol reactivity than those with no aggression or proactive aggression. Low cortisol levels have been associated with callous, unemotional traits, as seen in predatory aggression. Measuring cortisol levels clinically could help distinguish between callous, unemotional aggression and impulsive aggression.

Sex hormones and their precursor, dehydroepiandrosterone (DHEA), have also been studied in relation to pediatric aggression. High levels of DHEA-S, a more stable form of DHEA, have been measured in several studies in subjects with conduct disorder or pathological aggression and are associated with impulsive aggression. Fluctuations in testosterone levels may be associated with aggression and mood changes. High levels of testosterone were linked with aggressive behaviors in children and preadolescents. In adolescent boys, high testosterone concentrations were associated with provoked verbal and physical aggression, suggesting a link to reactive impulsive aggression.

Barzman D, Patel A, Sonnier L, Strawn J: Neuroendocrine aspects of pediatric aggression: can hormone measures be clinically useful? Neuropsychiatric Disease and Treatment 2010;6 (October 11):691–697. From Cincinnati Children’s Hospital Medical Center, Ohio; and other institutions. This review was not funded. The authors declared no conflicts of interest.

CBT Versus Combined Treatment for Anxiety

Children undergoing group cognitive-behavioral therapy for anxiety did equally well regardless of whether they received concurrent SSRI medication.

Background: The American Academy of Child and Adolescent Psychiatry Practice Parameter recommends combining CBT with drug treatment for moderate-to-severe anxiety disorders in children. Results of a few randomized trials suggest the combined modalities may be more effective than CBT alone. The present study was designed to examine the question in a naturalistic setting with clinically-referred children.

Methods: Study participants (n=48) were aged 8–13 years and had been referred to an outpatient mental health care program with a primary diagnosis of an anxiety disorder (excluding posttraumatic stress disorder, panic disorder, and obsessive-compulsive disorder). Specific anxiety diagnoses in the group were generalized anxiety disorder (62%); social phobia (17%); specific phobia (12%); separation anxiety disorder (7%); and anxiety disorder NOS (2%). Most children (69%) had more than 1 anxiety disorder diagnosis. Children with comorbid conditions other than anxiety were enrolled unless the condition would interfere with group participation. Manualized group CBT consisted of 12 weekly sessions that provided psychoeducation, relaxation exercises, and exposure and response prevention exercises. Parents participated in a separate simultaneous educational group. Treatment outcomes were measured using the child-
rated Multidimensional Anxiety Scale for Children (MASC) and the parent-rated Screen for Child Anxiety Related Emotional Disorders-Revised (SCARED-R). Scores were compared in the children concurrently treated with psychotropic medications for anxiety and those who were unmedicated.

**Results:** A total of 42 children completed the treatment protocol and were included in the analysis. All 6 children who withdrew had been assigned to the CBT-only group. Of the 42 children included in the outcome analysis, 13 received medication throughout group CBT. Drug treatment began a mean of 4 months (range, 1–9 months) before the start of group therapy. Eight patients received fluoxetine, 2 were taking sertraline, and 1 each received citalopram, fluvoxamine, and paroxetine. Doses were increased in 9 children during the CBT protocol. All patients completed at least 8 sessions, and more than 80% completed 10–12 sessions.

Pretreatment anxiety ratings were similar in medicated and unmedicated children. The length of time on medication before starting CBT was not associated with pretreatment scores. Both groups demonstrated significant reductions from pretreatment on self- and parent-rated measures of anxiety. MASC scores decreased from a mean of 56 to 41, and SCARED-R scores decreased from 49 to 29. Outcomes did not differ statistically between medicated and unmedicated children. Outcomes also did not differ between medicated children who did and did not undergo antidepressant dosage increases. Improvement was maintained at 4-month follow-up.

**Discussion:** The authors note that finding similar pretreatment anxiety scores in medicated and unmedicated children was unexpected given the duration of medication treatment prior to CBT enrollment. They speculate that some children may have been prescribed medications to reduce their anxiety sufficiently so that they could function in group therapy. Also unexpected, the vast majority of medicated children (92%) were male; the authors suggest gender differences in referral for pharmacotherapy should be investigated.

**Editor’s Note:** This study is limited by its small sample size and nonrandomized design. In addition, reasons for withdrawal were not included for the 6 patients (12%) who did not complete the protocol, and basing the evaluation on completers rather than using the intent-to-treat sample is an important shortcoming. The results appear to contradict previous clinical research, and further evaluations that meet controlled trial standards may be warranted in naturalistic patient samples.

Eichstedt J, Tobon J, Phoenix E, Wolfe V: Worried no more: the effects of medication status on treatment response to a CBT group for children with anxiety in a community setting. *Clinical Child Psychology and Psychiatry* 2010; doi 10.1177/1359104510366282. From London Health Sciences Centre, London, Ontario, Canada; and other institutions. Funded by London Health Sciences Centre; and the Lawson Health Research Institute. The authors did not include disclosure of potential conflicts of interest.

**Drug Trade Names:**
- citalopram—*Celexa*;
- fluoxetine—*Prozac*;
- fluvoxamine—*Luvox*;
- paroxetine—*Paxil*;
- sertraline—*Zoloft*

**Reference Guide**

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.