

# Some Children Outgrow ADHD, Imaging Shows

BY JANE SALODOF MACNEIL

SANTA FE, N.M. — Twenty years of brain imaging studies in children are leading National Institute of Mental Health investigators to explore whether they can distinguish youngsters who will outgrow attention-deficit/hyperactivity disorder from those for whom it will be a persistent problem.

This new work is built on evidence that normal brain development occurs with a 3-year delay in children with ADHD. In pilot data, the researchers have found a hint that the brains of youngsters who have “good” clinical outcomes compensate for this delay, whereas those of youngsters with “poor” outcomes take a different developmental trajectory.

“Approximately half of them grow up, and follow what their grandmothers said all along: ‘He will grow out of it,’” Dr. Judith L. Rapoport, chief of the Child Psychiatry Branch at the NIMH, told attendees at an annual psychiatric symposium sponsored by the University of Arizona.

Her group has accumulated more than 6,000 anatomic MRIs of children whose brains were scanned every 2 years starting at age 4 in a longitudinal study, she said. The subjects were not selected for any particular psychiatric condition, but 300 were subsequently diagnosed with ADHD. In addition, the investigators received 3,000 referrals of children with suspected childhood-onset schizophrenia, among whom it found and scanned 107 children with the rare disorder.

By mapping the normal course of cortical development, the study revealed a process of cortical thinning from ages 5 to 20 that can be seen in Dr. Rapoport’s words as “a back-to-front wave of cortical maturation” (PNAS 2004;101:8174-9; Nat. Neurosci. 1999;2:861-3). Comparison of high-intelligence children with those of high and average intelligence subsequently showed the children with high IQs had a developmental trajectory in which key measures were reached 2-3

years later than in the other children.

“We were simply astonished to find out the real difference was between the superior intelligence group and the rest, and it was in the frontal lobes,” Dr. Rapoport recalled, adding that this is “one example that later at least in some brain regions is not associated with deficit and may be associated with the opposite.”

The investigators were soon deluged with tales of geniuses who did not talk until late (Albert Einstein famously among them), she added, speculating that perhaps the late maturity coincided with more complexity in input to the brain. The cerebellum with its abundance of neurons may be “the last frontier in terms of therapy and understanding,” she suggested. It is the last part of the brain to mature, she noted, and the least heritable.

Subsequent work showed later cortical development in the brains of children with ADHD (PNAS 2007;104:19649-54), and that the trajectory of baseline thinning also differed in ADHD between children with better outcomes and those with poor outcomes. Among the findings were that brain asymmetry is not as

pronounced in ADHD as in non-ADHD children and that the right parietal cortex—a little region that “looks like a freckle”—develops differently in ADHD.

One study showed that cortical thickness “normalizes” in the right parietal cortex of 48 children with ADHD who have “good” outcomes. The difference at a key point in the developmental trajectory was statistically significant when these children were compared with 51 children with poor outcomes and to 161 healthy children without ADHD. The finding “suggests compensatory plastic response for good-outcome subjects,” Dr. Rapoport said of the ongoing study.

Further work suggests that some children with ADHD reach a developmental milestone by their adolescent years, but others do not.

She cautioned that her group has not published what it considers “just pilot data” in this regard, but has started to follow 80 hyperactive 5-year-olds in the hope of developing a predictive test based on brain development trajectories that will distinguish the children who are going to outgrow ADHD from “those who are going to continue to have problems.”

The study should produce results in about 5 years, she said, forecasting that such a test might help clinicians “single out people for whom resources are really needed, and let us relax more for people for whom, no matter what you do, it is going to turn out fine.”

Treating ADHD with stimulants remains controversial, and there is not good evidence supporting benefit from long-term use, she noted. Her group has found no difference in brain development trajectories when children on stimulants are compared with children not treated with stimulants, she said: “They were absolutely identical. A researcher couldn’t have planned it better in terms of the mean and standard deviation.”

That said, in the short term, she suggested, “Kids’ memories of grade school are happier [when given stimulants], because they weren’t at odds with everyone all the time.”

For now, Dr. Rapoport strongly discourages parents from spending money on brain imaging tests to diagnose ADHD. While useful for research, the tests currently available are unlikely to have sufficient sensitivity or specificity “that you would want anyone to pay for,” she said.

“I am sad to see that there are colleagues all over the country ... selling, in our already overtaxed health care system, brain imaging tests of various sorts for diagnosis of ADHD,” she lamented.

Dr. Rapoport also questioned whether the findings still to come will render premature the work going into the much-anticipated DSM-V.

She and her colleagues already have a theoretical classification scheme for DSM-VI that incorporates evidence of key cortical milestones occurring early in autism and late in ADHD when compared with normal development.

“At some point, you may be able to argue that brain development trajectories may turn out to be as important as any classification in psychiatry,” she said. ■

## Predicting Schizophrenia in Womb

Prenatal screening based on variations in the numbers of certain key genes might be able to identify the carriers of childhood-onset schizophrenia and other psychiatric disorders, according to Dr. Rapoport.

About 9% of children with childhood-onset schizophrenia have been found to have genetic abnormalities, Dr. Rapoport explained. When children with multiple copies or deletions of key genes are counted, the proportion with possible genetic markers rises to 36%.

Moreover, many of the genes also are implicated in autism. Both condi-

tions are associated with ahead-of-normal brain development, she said, and the timing of certain milestones might determine which of these or other disorders develops. Of note, three children referred to the team as possibly having childhood-onset schizophrenia subsequently developed bipolar disorder instead.

“I think the world is going to be stood on its head diagnostically when these things get sorted out,” Dr. Rapoport said, estimating that as many as 50% of children with early neurodevelopmental abnormalities could have copy number variants.

# ADHD Drug Use Tied to Higher Math, Reading Scores

BY RENÉE MATTHEWS

Children treated with medication for attention-deficit/hyperactivity disorder during their elementary school years score higher on standardized tests for mathematics and reading, compared with their ADHD peers who are not medicated, data from a longitudinal study of 594 children show.

However, the gains did not close the test-score gap between children with and without the condition, Richard M. Scheffler, Ph.D., of the University of California, Berkeley, and his colleagues reported.

They also noted that children

who were medicated for a longer time had reading scores of just over 5 points higher than those of their unmedicated peers. And although they did not find a significant interaction with gender, they did find that the medication-reading association was lower in children with an individualized education program than it was for those with no such program.

ADHD affects about 8% of school-aged children in the United States, of whom about 56% are treated with a prescription medication. The condition is marked by inattention and impulsivity, and by atypical levels of physical activity. This

population often also grapples with lower academic achievement, compared with non-ADHD peers, as well as higher grade retention, special education placement, and dropout rates. However, the association between medication use and academic achievement is “largely unknown,” the authors wrote (Pediatrics 2009;123:1272-9).

The investigators drew on data from the Early Childhood Longitudinal Study—Kindergarten Class of 1998-1999 (ECLS-K), which tracks the academic progress of a nationally representative sample of children who attended kindergarten in the United States dur-

ing that period. The full ECLS-K sample was 8,370, of whom 594 were diagnosed with ADHD. Of those with ADHD, 75% were boys, 71.6% were white, 12.2% black, 11.0% Hispanic, and 1.4% Asian/Pacific islander.

The data were collected at five waves between kindergarten and fifth grade—in the fall and spring of kindergarten and in the spring of the first, third, and fifth grades, over a 6-year period.

Dr. David Fassler, who was not involved with the study, said in an interview that the results are consistent with general clinical experience. However, be-

cause of the methodology used, he said, the results should be “interpreted with caution. For example, the authors rely on the parents’ reports of both diagnosis and medication,” said Dr. Fassler, a child and adolescent psychiatrist, and clinical professor of psychiatry at the University of Vermont, Burlington. “Nonetheless, I expect the findings will prove somewhat reassuring to parents and physicians evaluating treatment options for children with ADHD.”

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