

Q&A

An interview with Judith Rapoport, M.D.

ATTENTION! You have an impressive track record of research into attention deficit disorders. Share a bit of your research experiences, if you would, with our readers.

Dr. Rapoport: I started my research work in this area, a long time ago, when the vigorous research into stimulant drug treatment really began. Even though the first reports of the use of stimulant drugs appeared in the thirties, researchers learned much later that very rigorous research into the effects of stimulant drugs would be important. So for many years, between the 1972 all the way to the mid-1980s, we were doing a great deal of pharmacological research related to hyperactivity. It was our research, for example, that showed that children who are not hyperactive have the same kind of response to stimulants as do children who are hyperactive. Although we are strong believers in stimulant drugs as an effective treatment for ADD, this was a very important finding because it showed that response to stimulants could not be used as a diagnostic test for ADD or hyperactivity. At that time, a lot of pediatricians were indiscriminately telling parents that their child must be "brain damaged" because he or she would exhibit improved behavior when taking stimulant medications.

ATTENTION! Let us stop you here for a moment, because indeed the research you are describing is very significant, but it also often leads to confusion. Sometimes, that finding is used by people who seem to ignore the full body of research into ADD, who promote a mythology that ADD is a questionable disorder, and say, "See -- any child will improve if they take these medications"...

Dr. Rapoport: And that's not a valid criticism because any physician, in any discipline, who prescribes medication knows that there are two kinds of drugs. One kind is like aspirin. If you take an aspirin when your temperature is normal, it doesn't lower your temperature. Aspirin only works if you have a fever; then it normalizes your temperature. So, if you're feeling fine, you wouldn't end up with abnormally low body temperature if you took an aspirin. But there are also plenty of drugs that have the same effect on everybody but only make sense to take if you have a disorder. For example, anyone who takes insulin will experience a lowering of blood sugar levels regardless of whether that person is diabetic. The same is true with a diuretic. If you don't have heart disease or kidney disease, there are very few cases where you would want to take a diuretic. But if you did, you would be urinating constantly, even though you are not ill.

That's a very helpful distinction.

In fact, when these findings were published in Science Magazine and the Archives of General Psychiatry in the 1970s, they caused a fuss. We reported that these findings might suggest that -- since the action of the drug seemed similar for normal and hyperactive children -- its effect in the brain was probably "downstream" from any lesion or structural difference that was actually causing the hyperactivity.

And then you turned to your current research, using magnetic resonance imaging (MRI) techniques?

Not quite. Our group did a lot more work studying the effects of other medications besides methylphenidate. And we also spent time researching other disorders, including obsessive compulsive disorder and childhood schizophrenia.

About four years ago we were given access to an MRI machine, which allowed us to pursue a whole new direction of research into ADD. We were given an evening a week that we could run the MRI machine here. We had a chance to do what no private center outside the government could afford to do -- to get norms for brain development from age four to eighteen. Over the last four or five years, we have identified about 200 children who have absolutely no problems with attention, learning, or behavior. We have completed a study of about 60 males from four to eighteen and are halfway through a study with females. It is extremely expensive and time consuming. Why does that take five years? Because we have to screen about four children for every one that gets into the study, whether it's a control or a patient. With any neurobiological disorder, there is often strong comorbidity. Particularly with adolescents, we may see depression, substance abuse, or conduct disorder. And subtle brain abnormalities have been identified for other disorders. So for the purposes of this study, we tried to get a relatively pure group. We also needed to pull out any children from the control group who have close relatives with any neuropsychiatric problems.

The measurement is also time consuming. That takes about 30 hours per brain. We had people working full-time doing nothing but measuring the MRI tapes in three dimensions, one-millimeter slice by one-millimeter slice, outlining the brain image. It's very laborious. And remember, to identify sixty hyperactive children and sixty controls, we had to screen several hundred of each.

I am not saying that any parent reading this magazine should run out and get an MRI for their child. It's not a diagnostic tool for ADD. But it is a very good research tool.

What was your hypothesis going into this study?

Based on neuropsychology studies, studies with primates, and other contributing research, we did expect to find some abnormalities in the frontal lobe and basal ganglia of the brain. We now have the largest anatomic brain imaging study ever done using MRI. What we have found is that there are clear differences between the groups, and these differences are statistically significant. A radiologist would not read these scans as abnormal, but the differences are there.

What did you find?

We found localized differences between the brains of children who have ADD and those who do not. For example, there were no differences in the temporal lobes; that makes sense, because children with ADD tend to do pretty well on the types of tasks that are related to the temporal lobe functions. But parts of the anterior frontal lobe and the basal ganglia were smaller, particularly on the right side. That is very interesting, from an anatomical standpoint, because among normal children and adults, the right side is larger than the left side. So what we found in these boys with ADD was the lack of the larger right seen in "normals." These boys with ADD show a statistically significant difference in an important structure of the brain.

What does that add to our understanding of what is ADD or what causes ADD?

These findings clearly help place ADD in the neurobiological realm. They are an important contribution to our understanding of ADD as having a neurobiological component. In theoretical terms, it is a finding that makes sense because we now know that the kinds of things the frontal lobes do, they usually do in loops and circuits with the basal ganglia. What we used to think of as problems with frontal lobe functioning may actually be problems with this loop, though no neuropsychologist could tell you exactly what part.

So give us one functional example of frontal lobe functioning.

For any cerebral function that involves some sort of response inhibition, the basal ganglia often comes into play. So does planning complex sequences of actions

So we now know that frontal lobe activities, some of which include inhibition, take place as part of a loop involving the basal ganglia?

Absolutely. That's been known for a few years.

These findings, which are part of a paper that is in press at the Archives of General Psychiatry, will, I think, be among the most solid pieces of evidence to date pointing to a neurobiological component of ADD and could help ADD be more properly viewed as medical condition.

An exciting, potential study will be the twin study of ADD, where we can shine some light on whether these brain structure differences are genetic or environmental. If the twin study turns out the way I think it will, and if it's correct that ADD is related to some sort of non-genetic developmental influence then it could open up a another line of research. It is possible that some families are especially prone to some environmental influences that impact the developing fetal brain.

We are also building on our current findings by using the MRI as a brain imager to measure blood flow. It turns out that blood flow in the brain is related to the use of different parts of the brain. As the brain gets oxygenated and de-oxygenated, the magnetic properties change -- so we can get measures of brain activity using the MRI. We will be using this technology to measure brain activity in boys with ADD and those without ADD while they are performing activities that children with ADD are known to do poorly at, such as asking them to stop pressing a button when the correct target appears on a screen (often called a "reverse" CPT). Our hypothesis is that we will see less activation, particularly in the right frontal part of the brain in the boys who have ADD, which would, of course, be consistent with our anatomical MRI findings.

How does this work relate to some of the groundbreaking PET scan studies conducted by your colleague at NIMH, Dry. Alan Zametkin?

PET scans have two disadvantages that can be overcome with the MRI. One, is that PET scans use radiation so you can't use them with young children. The other is that, because they can be cumbersome and difficult to do correctly, it's been very hard to replicate findings. Dry. Zametkin landmark studies pointed to frontal lobe abnormalities in ADD. But, in many ways, the PET scan limits the work as it can not be used with children. We hope that the functional MRI studies will build upon his research.

We are also conducting an anatomical MRI study with girls, to see if we find the same differences in the anterior frontal lobe and the basal ganglia that we see in boys. We are

also replicating our anatomical MRI work with boys who have never been treated with stimulants to make sure that the differences in brain structure are not a result of the stimulant medication.

How long will it be before we hear about findings from your anatomical MRI studies with girls and boys who have not been treated with stimulants, and your research that uses MRI to measure brain activity?

I think by next summer we should have some preliminary results from the functional MRI work -- that's the study measuring blood flow and brain activity -- and by next fall, we should have results from the study of girls and the study of boys who haven't taken stimulant medications.