Brain and Mind  
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Judith L. Rapoport, MD  
Brain Development in Healthy, Hyperactive and Psychotic Children

Introduction by Richard Mayeux

Richard Mayeux: Our first speaker, Judith Rapoport, received her undergraduate degree in psychology from Swarthmore, her MD from Harvard, and was named chief of psychiatry at the National Institute of Mental Health in 1976, and she's been there since that time. She's also a clinical associate professor of pediatrics and psychiatry. Dr. Rapoport's research interests include obsessive-compulsive disorder, childhood schizophrenia, diagnoses in child psychiatry, biological aspects of pediatric psychiatry, and pediatric psychopharmacology. Her most recent interest is in brain imaging of the development disorders of brain and language. She has written extensively on her findings [and] is on the editorial board of many scientific journals. The title of her talk today will be "Brain Development and Childhood Psychopathology." Dr. Rapoport.

A Top-Down Approach

Judith L. Rapoport: Thank you very much. It's a real pleasure to be here and honor to be on this wonderful program as well as a great pleasure because I have many very good friends on the faculty and in the audience.

What I want to share with you today is very much a top-down approach to psychopathology. We have many disadvantages from the clinical point of view. We're not certain about our clinical categories, [and] we have complex diseases, as have already been mentioned, where even when genes are found, they tend typically to be of small effect. And we have another disadvantage known to clinicians of the time-consuming nature of the studies that are involved. Nevertheless, it turns out that there is some enormous hope owing to some of the new technology that lets old questions that have become perhaps tired or at least frustrated become totally new and exciting. And this rejuvenation of the field and the sea change that's taking place among clinicians like myself is really what I'd most like to convey.

As I was saying, technology changes everything, as you can see.
I think most of us have had a long-held assumption because of converging evidence from neuropsychology and other neurological exams that the more severe child psychiatric disorders do in fact reflect subtle neurodevelopmental impairment that someday could be reflected in abnormal brain development. But the advent of brain MRI which doesn't use any ionizing radiation and which most children tolerate without any adverse effects really permits the study of both normal and abnormal development, and it's hard to describe the way this entry into the brain has expanded all of our horizons, our dialogue with many other disciplines.

And what I just want to show you is a series of studies on normal and abnormal development, restricting the studies, although we've done many others, to anatomic brain development. And what's more, I'm not going to talk about the many other studies of cognitive development—clinical response, drug treatment, etcetera, family studies—that would accompany all of these because I want to just try to focus on one relatively simple theme.

The other thing that's important to point out is that I'm afraid my other presenters are not off the hook in terms of talking about brain development because, as you can see from this diagram, there's, starting with conception, an enormous number of different stages in the development of the brain from neurulation, neurogenesis, synaptogenesis, cell migration, programmed cell death, and so on. But what we did hope that we might see reflected was perhaps some sense—and this is inferring because I will only say once, but you should always assume I'm saying it—that we're unaware from an MRI level of what the cellular basis is of what we change. But we are prone to model building, and we assume that some of these may reflect competitive elimination of synapses, effect on dendritic axonal arborization, and, of course, trophic glial and vascular changes that go along. But then I'm also pretty much only going to show this very thin, pale ribbon that you see at the right of our study, which actually goes down perhaps to four years in some cases and up to now 24 or 25 in others. So the other presenters who were hoping that I would present more about brain development are still . . . this is the only thing to reflect the very many and important processes that I'm not addressing.

**MRI Studies of Normal Brain Development**

What we started to do 15 years ago was to have a large series of subjects with different disorders in healthy children simply to have a brain MRI every two years, with a machine that fortunately turned out not to be a lemon—and some of them are—that has lasted with us through all of this time, and this is simply a diagram to give you a feeling of the healthy database which so expands every month that it's already several months behind. But the pink lines are females and the blue lines are males, and if a dot is connected it means that this person has had a large number of rescans. And for each of our cohorts, we have some comparable kind of data, and the patients also had scans and rescans every two years.
And what made our life possible was at the same time a wonderful package for measurement of brain MRIs was being developed. There are now many competing packages, but at the time when we started, one of the most prominent—and the one we have stuck with for some of these studies—has been that from the Montreal Neurological Institute, where they combined two different approaches to measuring brains, one that simply at the top uses prior information from what's where in the brain, from neuroanatomy, and another one that simply classifies tissue of brain—gray matter, white matter, or CSF—and by marrying these two gets more information than you're likely to from either one alone. Most important to us, since we now have more than 5,000 scans across our various studies, it is fully automated, and their supercomputer can work away doing hundreds on a weekend while we're gainfully occupied doing something else. That's a very endearing characteristic of this system.

As you can see from the top left-hand corner, there's much to be gained from prospective studies. Your brain size varies more than your shoe size or your glove size, and as a result when you have brain data across samples, cross-sectional data—just comparing at any point in time a control group, for example, and a patient group—most of the studies, because of the noise within differences, are hopelessly underpowered to be able to make any statement about diagnostic differences, whereas when you start to include your longitudinal data and some singleton data, thanks to statistical advances what you can start to see are that these curves are in fact not straight. They're nonlinear, at least some of them are, and you start to see all sorts of interesting things.

This is parts of the brain, crude parts in this study, frontal gray, parietal gray, temporal gray matter, and several things come out here. First of all, that if you have a large number of subjects, you start to see that different parts of the brain mature at different times, with the temporal lobe maturing significantly later than the other parts. Interestingly—and these are also statistically significant—the pink reflects the females in the group, and as you can see, there's also some timing difference which for frontal and parietal are also statistically significant. A talk that I am not going to give now, but could very entertainingly and easily on some other occasion, are sex differences in brain development, which are very provocative and may well bear in part on I think some of the very interesting data that Dr. Rutter is likely to talk about. At any rate, the strength of having this normative data has been extremely important to us.

A lot of other spin-offs from this study have come out—for example, what's the relationship to intelligence. And the interesting part is that while IQ is related to the height of the slope—that is, how the volume of almost any structure . . . it has no effect on the shape. We had wonderful hypotheses that intelligence might relate to either the steepness or the ascending part of the steepness of . . . no such luck, it remains exactly parallel.
We speculate, of course, about what may relate to the differences underlying and the molecular geneticists in the audience, I think, could come up with pages of lists of candidate processes, signaling systems and so on, that could possibly be involved. But I just want to mention that the pioneering work of Peter Huttenlocher and his students . . . looking at the very scant number of postmortem brains across childhood and adolescence showing both the rate and some regional differences across different parts of the brain, both for the timing of development and, more important, for the timing of the decrease with the overproduction of synapses to healthy adult levels.

Another thing that we've learned—not shown on the diagram that I just showed you—are the hordes of identical and fraternal twins, who are also going through this process, so that we are in the process of studying the heritability of the slopes for different parts of brain development at different times, which we expect will be different, the heritability for different brain structures at different times during this age period. But some things are clearly heavily genetic—for example, the corpus callosum, some white matter structures, easily you can tell, even if pictures fall on the floor, you can know which twin to put together easily from some structures. And even with our limited amount of twin data, from this old slide, the heritability is fairly high for most of the structures, even in childhood. So the main point so far is just to tell you that prospective studies give a unique sensitivity which we've never had before, that different brain regions develop at different times, and that there's some regional difference in heritability.

**MRI Studies of Child-Onset Schizophrenia**

Now having had now my very short course in what we've learned about normal brain development, I want to go on to talk about some of the disorders that we've been tackling. I'll never do justice to the issues with the brain and schizophrenia because almost every part of the brain that's been examined has proven to have some kind of abnormality of this devastating disease that is so expensive to society and for which the cause is unknown.

A child psychiatrist usually doesn't study childhood-onset schizophrenia, but we have been recruiting a rare form of the disorder because it was a unique way to study brain development during an age when there are major organizational changes. I think it should be obvious to people here that since the typical age of onset of schizophrenia is the early twenties, that obviously you won't know what's happening in the brain in adolescence unless you select this rare early sort. In addition, early-onset populations are traditionally a very good way to look for genes, but I won't go into that in very much detail.

The point of this is just to say that, as seen for adult disorder, our children who had the mean age of onset of schizophrenia of age ten had a smaller total brain, even at the time we first met them, had larger brain ventricles, and these represent findings in adult patients. But where we depart from the literature on the adult
patients, as you'll see, is that until fairly recently schizophrenia in adults was hypothesized to be an early fixed lesion without progression. One of the things that was clear to us from our child schizophrenia population is that they had all sorts of problems before they actually became psychotic at age 10, and that a very . . . this Venn diagram indicates that a large number of them had overlapping problems of social and language and motor functioning, such that a fair number of them were evaluated for autism early on. And while autism and schizophrenia, I think, are well-validated, distinct disorders, for whatever reason early in their development, there were many similarities. And in fact about 20 percent might be considered to have still some pervasive developmental disorder together with autism. But the real point of showing you this is that it's a sign to us that there was a worse hit, so to speak, to early brain development than the typical adult-onset patient had even earlier, before they became psychotic.

And this is my diagram now to show our data set, now considerably increased, for the childhood-onset population, and not shown here is a comparable set for the brain development of their healthy siblings, who are also under study.

Now there have been all sorts of models, hypothetical progression of brains, to do with degenerative disorder and developmental disorder, and this slide is just simply to make it easy for me to say that there have been hypotheses about tissue loss representing an access over the mean, perhaps representing neurodevelopmental disorders. Whereas if it's excessive, it happens later, it's a degenerative disorder. Much of what's being learned, I think, entirely blurs this distinction, and what I want to add is that there's a whole other line remaining to be written here that I think are diagnostically distinct.

So again using the Montreal program initially, what we did was we looked for change, and this is a very crude measure of just total gray matter—frontal gray, temporal gray—in our prospective studies of the schizophrenic children, compared to the yellow being community controls, the normative group that I talked about first. And the blue is a very important contrast group because they're other children, who we're also following, who have transient psychotic symptoms but mostly behavioral dyscontrol and, most importantly, were on the identical medications throughout these years, so that they represent a treatment control. And the point here is that across several areas, but curiously particularly in the back of the brain with the parietal gray, what we were seeing was a very large percent change across adolescence, to a remarkable degree that clearly is of a level that you might even see in Alzheimer's disease, so we were very careful to make sure we were actually doing this right. And, in fact, there have been a few slides . . . this is something called an effect-size comparison, where the red arrow is the size of what we were seeing in adolescence for this group . . . but there have been a handful of studies with adult patients, and the point is that it's very little when you do see progression, relatively speaking, in older patients with schizophrenia.
But here's where a collaboration with UCLA came in, because a method that lets you align brains so that they look more like real brains and pictures of brains allows you to actually visualize changes in brains because you can line up the invariant sulci and then you can actually subtract brains from one group to another. And what we found is that when we looked at the earliest development compared to their yoked control group, you see the red, which represents tissue loss relative to the controls, is mostly in the back of the brain, whereas later at the end of adolescence, you see something actually quite different. And this was the beginning of my career as a moviemaker at the NIH. In childhood I, like probably many of you, were fascinated that you could grow plants in ultraviolet and infrared light, and as a result make movies of plant growth. And even though it takes us 15 years for us, and only two or three weeks for the narcissus, we have actually been able to—15 years later—reap the benefit of these various projects that I've been mentioning and actually study what happens when a child develops schizophrenia. And if anyone ever doubted that this is a brain disease, this is not what's happening in the medication-matched controls, not being shown, and interestingly the area that by the end of adolescence in fact looks the healthiest still is that area, the dorsolateral prefrontal cortex, is about the one that in adults people make the most fuss about, but that isn't where it started. And this was really an arresting sight. And on the medial side, it's not quite the same, it's like a curtain dropping. So remember these two patterns: the back-to-front wave of loss and the curtain dropping from the medial view.

Now, of course, a question that would, I think, occur to most people is, How does this compare to the normal rate? Well, no one ever made a movie of normal development, and that poses certain challenges because with the schizophrenia map that you just saw, we could at each stage, every two years, subtract our patients from their controls, and then in Hollywood cartoon style make a movie of the changes. Well, the controls are the controls; you can't subtract them to anything, from anybody, but you can relate them to an absolute level, say at the age of 4. And so then you can go on to create a movie, and don't be confused here by the fact that as they get old, between 5 and 20, it's blue. It's that the normal movie looks so much like the schizophrenia movie except at a much lower level that I reversed the colors in order to keep them straight. So for the normal movie, remember that blue is loss over time, whereas for the schizophrenia movie . . . so on the left top is the healthy control movie across this age with a back-to-front wave of loss, and that's the schizophrenia one that's just gone. Now notice the bottom left is the medial normal movie with something of a curtain coming down, and then on the bottom right, which I think it will do by itself . . . well, you get the idea. So of course this is now a second interesting fact, and with my captive population of molecular geneticists in this audience, something a child psychiatrist doesn't always get to have, I think this is very tempting to talk about how the game might be up on a normal process, possibly related to synaptic development, that is out of control in the schizophrenic sample.
Gene Expression in Child-Onset Schizophrenia

Another question, of course, was how is this related to genes. Not going into any detail, but, of course, it's tempting to look at the various candidate genes which have recently been so surprisingly and increasingly well-replicated in schizophrenia. And what we're finding is that in fact a number of them, a surprising number of them, give a diagnostic signal within our not terribly large child sample, since we only have eighty-odd probands, we have all their family members in our genetic studies of schizophrenia. But what was particularly interesting to us was that the gene GAD1, which codes for GAD67 expression, that a series of postmortem studies have shown decreased expression of GAD67 in the brain, and, in fact, this is one of the genes found from brain-expression studies, not from positional cloning. And, in fact, the overtransmitted allele is, in fact, associated with steeper decline, particularly in the frontal lobe. But, and here comes my next message here, that before we leap to thinking that we know what these things mean, what we've been struck by was in fact . . . here I'm showing you this incredible tissue loss, and this is where the clinical end of the study comes in . . . the pink part, the right-most part of this age curve, which is just giving full-scale IQ across the study, and starting with the pink color is where they took part in the studies, that there's no loss of IQ for our population in spite of these horrendous change. And much more interesting is that by our four most typical measures of symptoms in schizophrenia—positive symptoms, negative symptoms, overall functioning, total symptoms—for our subjects, in fact, that the gray-matter loss was associated with clinical improvement.

Now this is one of the reasons why I think the clinical part of these brain changes is so important, because when you look at postmortem brain changes in any disorder, you never know what may be restitutive or plastic responses to abnormalities. And it's not too great a stretch of the imagination to think that since in normal adolescents presumably—at least we all like to think that it was the less-used or possibly malfunctioning synapses that get eliminated—it may well be that this is simply an increased reaction to the numerous malfunctioning processes likely to be going on in schizophrenia. This is, of course, wild speculation, far beyond the level of the data that I'm collecting. But I think it's very important, since when we first published this, we were contacted by a number of pharmaceutical firms wanting to know should this be a target of treatment, and the answer is, I don't think you can tell.

We were relieved to find that this loss—and the red is again the loss, the rate going down compared to healthy control group across adolescence—is that this loss plateaus and that, in fact, by the time these patients are 30 or so, they are unmistakable in terms of brain imaging from your typical adult-onset patient, and they're unmistakable in many other ways, including all the family markers of heritability and many biological and psychological markers.
Conclusions

So to summarize this, there's this progressive back-to-front wave of loss. It may be an exaggeration of the normal developmental pattern, and I would love speculations from geneticist colleagues in the audience. It is associated with candidate gene risk but may have a restitutive function, and that we are very interested in . . . and this is a trailer for a movie, not one I'm going to show because it isn't ready yet . . . but we're very carefully following the functioning of the healthy siblings, whose scans we also have every two years in order to see whether or not any differential decline—and I think there will be some—is related to either genetic risk or their functioning, and if it is related to their functioning does it go in a good or bad direction?

[A portion of the transcript including unpublished results has been removed at the request of the speaker.]

But the main point is that, I think, we've come a long way to bridging what child psychiatrists worry about and live with every day and model systems in our head and relating to preclinical work. I think it validates to some extent the DSM people. It's become very fashionable to say very critical things about ICD and DSM, but in a crude way, I think, it shows considerable validation for these unknown and as yet largely unexplained disorders. And I think clinical studies are going to be very important to interpret brain abnormalities, many of which are probably plastic studies, and that these are also proving very useful and phenotypes in our own genetic studies.

And thank you very much for your attention.