Brain and Mind

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Sir Michael Rutter, MD
Neurodevelopmental Disorders

Introduction by Richard Mayeux

Richard Mayeux: I'd like to start the second half of the program. I'll start off by introducing Professor Sir Michael Rutter, who's professor of developmental psychopathology at the Institute for Psychiatry at Kings College, London. He was a consultant scientist at the Maudsley Hospital from 1966 to 1998, and professor of child psychiatry at the Institute for Psychiatry from '73 to 1998. He set up the Medical Research Council Child Psychiatry Research Unit in 1984 and the Social, Genetic and Developmental Psychiatry Research Centre ten years later, being the honorary director of both until October of 1998. His research has included the genetics of autism, study of both school and environmental influences on children's behavior. He also has a special interest in the interplay between genetics and psychosocial risk factors. He's led a major study into the effect of severe deprivation on Romanian orphans adopted into Britain. He's now entering the third phase in which subjects were followed up to an age of 15. He's well published and is currently the deputy chairman of the Wellcome Trust. Dr. Rutter.

Features of Neurodevelopmental Disorders

Michael Rutter: Well thank you very much indeed. It's a great pleasure to be here. The organizers may feel they've invited me here to give a talk, but I feel I've been invited here to expand my science education, because today's talks have certainly done that.

I'm following on in a way that I hope will show some continuity with what's gone before. The approaches are somewhat different, one in that I'm taking a group of different disorders that seem to have some features in common in order to look at what we may learn from them. I will be asking some questions along the way about continuities and discontinuities between normality and disorder. I will be bringing in a range of areas of science, not just genetics and functional imaging, but also epidemiology and cognitive neuroscience. And I will be emphasizing, and indeed several of the speakers have, that science should not be viewed as a collection of things we know, as a knowledge base, but rather as a process, as a means of

solving problems. And accordingly I will be emphasizing the puzzles and challenges that remain as much as the achievements so far.

So let's just look at the concept of neurodevelopmental disorders. They involve delays or deviance in maturationally influenced psychological features, in other words, features that cannot develop unless the necessary neural structure is available. They are disorders, but unlike most psychiatric conditions the course of disorder is not marked by remissions and relapses. The impairment on the whole lessens with age, and that is a characteristic of this group, but the disorder often persists into adulthood, and so it's not just a normal variation. The disorders involve in all cases some degree of specific or general cognitive impairment, and there is a tendency for overlap among these different neurodevelopmental disorders. They have things in common, but they also have some quite striking differences. In all cases the genetic influences are quite strong, but there is evidence that environmental factors are also contributory. And lastly the disorders all show a marked male preponderance.

The four case examples I'm using are specific language impairment, dyslexia, ADHD, and autism-spectrum disorders. That's not all the conditions one could put in this group, but it's the ones I'm going to talk about.

There are things that are reasonably well established. The diagnoses at the core have been shown to be reliable and valid. We know there's a substantial degree of persistence into adult life, and moreover we know that each of these conditions carries important risks for other forms of social and psychological malfunction. And we know that there's a degree of specificity in the associated cognitive deficits. But—I've had to move into a smaller print here—there are a huge number of matters of continuing uncertainty. So that, although the core diagnoses are well established, the boundaries of all four of these conditions remain quite uncertain. Because of that it's unclear whether the disorders should be conceptualized as primarily categorical or dimensional in nature. And that dilemma remains even though there are, for example, imaging abnormalities of a well-documented kind in all four cases. Although there is, through imaging and other modes of investigation, consistent evidence on the existence of neural abnormalities, the evidence is surprisingly inconsistent on their nature, which forces one to think as to what sort of disorder we're dealing with. Fourthly, although there is consistent evidence on the strength of genetic influences, definite susceptibility genes have not yet been identified. And fifthly, there are major uncertainties on the importance and nature of environmental influences. These are, with a few exceptions, multifactorial disorders, so that we know there are multiple genes involved, and the expectation is of multiple environmental influences as well, but we have very limited knowledge on just what those might be

Research on Cognitive Features

Well just a few examples of findings. I pick on reading disability because there were claims for a while that this wasn't actually as common as it was supposed to be in males. This is a bringing together of four very large epidemiological studies, each of which shows that there is indeed about a 2-to-1 male preponderance. And that is true of other studies as well.

Now let's focus on autism for a moment. There is a lot of research showing not only the presence of cognitive features in autism but also evidence that these are pretty basic to the nature of the disorder. The problem, however, is that we have half a dozen of these. The theory-of-mind deficit, about which I'll say more in a minute, is undoubtedly the best-established, and which is the strongest and most specific of the corollaries, but a lack of central coherence, which I will comment a bit more about in a minute, is also quite strongly associated.

Much less investigated in terms of its implications for autism are splinter skills or idiot-savant skills. The individuals, who, while generally handicapped in their mental functioning, are astonishingly good at some individual skill. These are not entirely confined to individuals with autistic-spectrum disorders but they are much commoner in this group than in any other group of conditions, and if one understood what this meant, it would, I think, provide important clues to the condition as a whole. In addition there are pragmatic language deficits, there are, particularly in early infancy, joint-attention deficits, and, rather less specifically, executive-planning deficits.

So what do we mean by theory of mind? So I go back to the classic experiment published by Baron-Cohen and colleagues in 1985 in which you have two figures, Sally and Ann, and one of them places her object in this basket. She then goes out for a walk, and then while she's out the other child takes the object from the basket and puts it in her own box. And then the question is, When the girl who's been out of the room comes back, where will she look for her object? Will she look where it was when she put it there, or will she look where it in fact now is? In other words, can she think into the mind of somebody else? And I'll come back to findings on that in a minute.

The central coherence is a quite different notion which deals with the fact that all of us tend to look at pictures from an overall gestalt point of view, and we find it quite difficult to break down gestalt to look at something that isn't part of the overall impression. So this is an old test, embedded figures test, in which you see the pram at the top and the question is to find the triangle, or in the bottom a rocking horse to find the house. And the findings on this are that individuals with autism are much better at that than are normal individuals.

Now the association of these has been particularly with autism, and there's now a large literature on this with highly replicated findings. But a follow-up study by Judy Clegg and others, the group that we first studied when they were young children, who comprised boys with a developmental language disorder involving receptive language but who did not in childhood show any autistic features. These are individuals who are now in their midthirties and what you see here is the findings from two tests of theory of mind, the awkward-moments tests, and strange stories, and in each case the developmental language disorder group, this column here, are scoring way below their siblings, and way below general population IQ-matched controls, and those are obviously highly significant differences. So we have here a group of individuals who were not autistic, who had a language disorder, and who then in adult life in terms of theory of mind tests are somewhat comparable. Their deficits are less in degree than one ordinarily finds in autism, but very similar in kind.

We'll come back to that group in a moment, but let me turn to a different research strategy which is now looking at what happens to these individuals over time, starting with autism. And this is a follow-up by Pat Howland and others looking at individuals with autism, all of whom had a nonverbal IQ of at least 70, in other words, within the normal range. And this is showing what they were like in adult life. And you can see there is a small group here who are doing very well, they're living independently, they are having some friendships, and are generally okay. But let's look here. We have here a group, not quite half, who despite a normal nonverbal IQ are basically functioning very poorly in all respects. The groups in the middle are sort of intermediate.

So the question then here is, here we have the group of individuals with autism with the best prognosis, as demonstrated by umpteen studies including our own, and yet two-fifths-plus of them are still severely malfunctioning in adult life. And it's not at all clear why that should be so. In passing I would simply say that their level of IQ within the normal range was of no predictive value. IQ was predictive in the broader group in the sense that those with severe mental retardation did uniformly badly and those with mild retardation were sort of intermediate. But no association within this group.

Let's come back now to the young people with developmental language disorders. These are the group now, Judy Clegg's follow-up, in mid-adult life, and a group remember who were selected for showing no autistic features in early childhood, and indeed as far as one could tell socially were okay. But look at those who had a normal range of friendships, less than half, the proportion who'd married or in a regular cohabitation, less than a third. And the schizotypy score was also well up, compared now with the siblings, all of whom had a normal range of friendships, all of whom had married and had a normal low schizotypy score. So we have a dilemma here of a group defined in terms of an absence of social problems in childhood who have become more socially impaired in adult life, or have they? That's to say they are more impaired in adult life but is that because they've got

worse, or is it simply that the social demands have gone up? Well it's difficult to be sure, but it seems likely that it's the social demands that have gone up in terms of intense friendships, love relationships and the like, rather than deterioration.

Genetic-Research Findings

Okay let's switch to genetics, what does that tell us? As I've mentioned, the findings on all four of these groups is of a strong genetic influence. This is the combined two British twin studies, looking at the percent with an autism-spectrum disorder in terms of the monozygotic co-twin on the left, the dizygotic co-twin, the bluey-green in the middle, and red the general population. So that the increased risk in relation to the general population or the MZ-DZ difference is enormous. The precise heritability that gives rise to depends a little bit on the assumptions you make about the population base rate, but the estimates would be between twenty and one hundred. So it is a huge increase.

But one of the things that came out of the first small-scale twin study that Susan Folstein and I did was that, although there was concordant for autism, there was also an association with what we came to call the broader phenotype, meaning individuals who did not show the major handicap in the disorder of autism, but in terms of their social and communicative functioning, repetitive stereotype behaviors, were very similar. And if you exclude the pairs that are concordant for autism and focus only on the broader phenotype, what you see here is that the broader phenotype similarly has a strong genetic liability. And so back in the seventies then this was the first indication that we needed to think in terms of the genetic liability for autism as going well beyond autism as it was conceptualized at that time. This is looking at a family study. Here of course you can't be sure what's genetic and what's environmental, but the point is you land up with exactly the same pattern. Comparison here between families with a proband with autism and a family with Down syndrome proband. And that whether you're looking at autism or the broader phenotype a big difference between the two.

What about the other conditions? Well this is the twin study undertaken by Dorothy Bishop and colleagues and she approached it in the same sort of frame of mind as we did, focusing initially on serious specific-language disorder as conceptualized at the time. And as you can see there is indeed a big difference between monozygotic and dizygotic pairs indicating a strong heritability for developmental language disorder. But what came as a surprise at that time was that within the monozygotic pairs to a much greater extent than in the dizygotic pairs you were seeing a whole variety of language and cognitive problems of a kind and a degree that fell well short of accepted diagnostic criteria, whereas this was less so in the dizygotic pairs. So the implication once more is that there is a strong genetic influence, but it is applying to a broader group than the conventional diagnosis.

The same applies to the other conditions, but let me jump ahead to just say a word or two on linkage findings. In terms of autism there are partially replicated linkage

findings for areas on three chromosomes. I say partially replicated because of the usual problem about knowing what you require for a replication. It is quite striking that in almost all cases the half-a-dozen international consortia come up with much the same answer. But the problem is it's not in precisely the same spot on the chromosome, and the strength of the linkage varies.

For dyslexia there is rather more in the way of replication, predominantly for loci on 6 and 15 although there are others as well. If we turn to ADHD, the findings are of at least two genes where there either association or linkage and there is replication and there is relevant experimental evidence in support. So it seems very reasonable to suppose that they are playing a role, but the effects are quite small and that it's difficult to know whether to be discouraged by the fact that the only genome-wide scans haven't actually been able to find these genes associated with ADHD, or to be encouraged by the leads that these are genes associated in some way with the dopaminergic system. I mention that because one of the interests in what one finds with susceptibility genes is not finding the genes, which is no big deal—I mean it's proved incredibly difficult—but having found them it doesn't tell you anything very much until you've got some notion of what they do. But with respect to both ADHD and schizophrenia they do link in with evidence on neurotransmitters.

One of the interests in relation to all of these disorders is whether it might be better to focus on so-called endophenotypes rather than the disorder as such, meaning by an endophenotype something which is defined in functional terms in ways that are genetically influenced, and which are related to the disorder but are not the symptoms of the disorder. And of course in ADHD there's quite a substantial body of evidence on cognitive findings and Castellanos and Tannock have put forward notions of three features that they suggest are good candidates for treating as endophenotypes because there is experimental evidence tying them in with the dopaminergic system and with functional-imaging findings.

Functional-Imaging Studies

Which brings me on to say a word on functional-imaging studies. This is a rapidly growing literature and it would make no sense to try and summarize all the findings. So instead let me just give a very simplified version of the rationale for using functional imaging in relation to disorder. Functional imaging actually has a range of purposes, so I'm focusing on one particular approach.

So here in relation to disorders such as neurodevelopmental disorders, where the centrality of cognitive abnormalities is so crucial one needs to choose a cognitive process of interest, mentalizing would be a key example, and then select a task to tap that process, which would be one of the various tests of theory of mind. But we need to choose an easy version of the task so that everyone can be expected to be able to do it, and to select a high-functioning sample with the condition being investigated. So the notion is not to show that the individuals can't do the task, it's

actually the opposite way 'round, it's to focus on subgroups who, provided the task is easy enough, can do the task and ask are they solving the cognitive problem in the same way as normal individuals?

So how do you do that? Well you compare cases and controls with respect to brain activity during those tasks and compared with various control tasks, and the question then is whether cases and controls are using the same parts of the brain in tackling the same tasks. There are various other bits that need to be added into that so that an experimental approach in which you can test whether any differences lie in differences in familiarity with the task as distinct from capacity on the task also need to be done. But let me just leap ahead to the findings.

They're interesting but puzzling. So that face recognition is one of the abnormalities that has been well associated with autism, and in normal individuals face recognition is associated with activation of the fusiform face area, whereas in individuals with autism that tends not to be so. Rather there is activation in areas that would in normals be used for processing objects rather than faces. I should say in passing that the part of the brain used for processing faces is ordinarily different from those for other objects. In theory of mind, normal individuals' mentalizing processes associated with activation of both the prefrontal and the temporal areas, whereas in individuals with autism that is less so, there is some of that. But what is more striking is reduced connectivity between the extrastriate regions and the superior temporal sulcus.

Now two things, as it were, emerge from that. The first is that you don't land up with answers which show that this part of the brain is malfunctioning in autism, because it depends which task you're looking at you land up with different answers. And the second is that it appears that it's not so much that there are various areas that are malfunctioning, but that in some way it's the connectivity across areas that is the striking feature. So that Chris Frith has suggested, as have others, that the early sensory-processing areas activate normally, but the later sensory-processing areas are less active. That's to say the dealing with the initial stimuli is okay but what you do in drawing inferences about those stimuli is the problem. And he speculated that this may mean that high-level top-down signaling fails to modulate connectivity, and that this is possibly due to a lack of neuron pruning accompanied by an increase in head size. As Judy Rapoport mentioned, it is striking that head size in autism is often increased and that this appears to develop during the preschool years. Whether it plateaus is more controversial.

Let me turn now to dyslexia and reading, dealing here with a follow-up study by Maggie Snowling and others, which was taking a family high-risk group, i.e., with a loading for dyslexia in the families and a group of controls, and following them up from three to eight years. And what you can see here is that the proportion who are showing reading difficulties in the family risk group is well above the controls; indeed it's a majority. And together with evidence there's not time to present again, the implication here is that we are dealing with something that is distributed much

more widely than the traditional diagnostic concept would lead one to believe. She has suggested—Maggie Snowling that is—that in familial dyslexia that you have a deficit in verbal-association learning, that's what she postulates as the basic handicap, and it's when that's combined with a deficit in oral language that you actually get the functional impairment in reading so that whether or not reading disability occurs depends on the degree to which both these skills are impaired; it is related to the presence or absence of development of compensatory strategies and also the time and quality of teaching, both in preschool and school.

In terms of specific language impairment it's not quite so clear what is happening, and indeed somewhat puzzlingly the findings from the genetic evidence that Dorothy Bishop has dealt with—not just the study I referred to earlier but also other data—suggesting that there may be a different route for the genetic influences and the environmental influences. For a whole variety of reasons that would be quite surprising, but if indeed turned out to be true would be very important.

Conclusions and Challenges

So let me pull things together with just a small set of conclusions. We start with the evidence that neurodevelopmental disorders constitute an extremely important and interesting group of seriously handicapping conditions about which we know a good deal. They have two very important things in common, well they have more than two, but especially two. The first is the marked male preponderance, and the second is the association with specific or general cognitive deficits, as well as the general features of early onset, persistence into adult life, and lack of remissions or relapses. So that the question that comes up with the male preponderance is, Is it simply coincidental that the disorders showing a male preponderance are almost all neurodevelopmental disorders, in marked contrast to those showing a female preponderance which are basically adolescent onset, emotional disorders, eating disorders, and things of this kind? The theories mainly deal with one of these conditions at a time, and come up with different hypotheses for each condition. Well I think the bringing together of disorders tells you that of course there may well be, probably are, specificities, but it would be a very strange coincidence if this group of disorders, the male preponderance, didn't have something in common.

The association with specific or general cognitive deficits, although the details of the deficits are different, there is overlap; the theory of mind I mentioned in relation to specific-language impairment and autism, but there are others I could mention, so that the suggestion that I would want to leave you with is that we have various ways of tackling these problems. Some, we've heard important things during the day, approach it, as it were, from the basic science end, some approach it from the point of view of looking at normal development, some from a strong focus on an individual disorder. All of those are worthwhile, and indeed all of those are going on with autism, but in addition I think going across disorders may be valuable.

But in saying that I've got to come back to the fact there are important differences among this group of disorders. And so we have to deal with the question of the commonalties and the differences and both have to be taken on board, and of course the usual question, are these two sides of the same coin or are we dealing with a different set of factors that explain the heterogeneity?

Now in all cases it seems likely that we are dealing with a systems disorder of one kind. I've emphasized that particularly in relation to autism with respect to the functional-imaging findings, but it actually comes up somewhat similarly in dyslexia, for example. But the question then is, What sort of systems disorder? And with the exception of ADHD, what is striking is that drugs have proved remarkably lacking in benefit. There are some drugs that in some children make some difference, but if you compare it with ADHD or depression or schizophrenia or bipolar disorder one has to say, here we have what all of us think are systems disorder, and yet we find nothing of any great interest in drugs that affect neurotransmitters. Well maybe we're looking at the wrong neurotransmitters. But it is still a puzzle.

And so, as I say, it's only in the case of ADHD is there a substantial response to medication, and that does make it different from the other disorders. Of course with ADHD we have the problem, as we have throughout the whole of internal medicine, that we know a great deal about group responses to treatments, and the same applies to psychological treatments or medication, but we know much less about why there's such individual variation, that even with the most powerful drugs there are individuals who don't respond and individuals who do respond, and we have a very limited leverage on what that is due to. Pharmacogenetics may provide an answer, but it hasn't as yet. And of course there are similar differences in terms of side effects.

Genetics I think is going to be helpful in leading us forward in clues as to what biological studies need to be undertaken, and it will be very important that genetic research goes hand-in-hand with the rest of biological studies, in both basic science and clinical neuroscience, because the genes themselves are of interest only once we know what they do at a molecular level, but then is the further issue as to how it leads on from the effects on proteins to the phenotype, and that's an even bigger set of issues and we're at a point I think when we can see the road down which we want to go, but we're quite a long way from seeing where we're going to land up.

And on that point I will end. Thank you.

Questions and Answers

Eric Kandel: I found that just fascinating. I was particularly taken by three of your remarks. One is that this is an inappropriateness of connection that you have in autism, so it's a misconnection syndrome, and contrast it to the disconnection

syndrome that [inaudible] was speaking about to the imaging studies which suggest that when autistic kids look at faces they see objects, and third the lack of response to drugs. So it seems to me this suggests if the misconnection idea is correct that perhaps the defect is really quite specific, and it isn't early stages of visual processing versus late stage, it's the particular pathway that is concerned with object recognition. So one would predict, for example, that these children would have no difficulty in recognizing objects in space or movement of objects in space, that the pathway concerned with where objects are would be intact, number one. And number two is if it in fact is a misconnection syndrome, I don't know why one would expect modulators of transmission to affect it. This presumably is sort of a Tom Jessell problem; it's how neurons find each other that maybe is an abnormality in cell recognition, cell adhesion molecules, or something like that.

Michael Rutter: Well I agree. Those are very perceptive remarks, as always. The reason for emphasizing the neurotransmitters is that virtually everybody has assumed that's where the answer lies. But I agree with you that for the reasons you put forward that actually doesn't seem very likely, and if Tom at the next time there's a symposium, but I hope we don't have to wait 250 years, can find an answer to what is causing these misconnections, that would be great, I will be back.

[Question inaudible.]

Well that's a good question, but it's actually a very difficult question to . . . The question is, Of those four disorders which are the ones that are most affected by psychosocial influences, and affected by detriments in self-esteem and the like?

The problem is that you will probably pick out ADHD, I suppose, but the dilemma then is, Are the psychosocial factors which are associated with malfunctioning socially in middle childhood and adolescence telling you about psychosocial influences as they impinge on the hyperactivity as it was present in early childhood, or rather on the transition to the conduct problems and so on that follows? It pretty certainly is the transition to conduct problems. Whether in addition there is a causal effect on the hyperactivity itself I don't know. But let me throw in two findings which were puzzles to me. I've never understood, I must say, why psychologists spend most of their time being firmly committed to showing that they were right. My interest in research is understanding why I was wrong, and I am keen to say, I've had several examples in my career of being spectacularly wrong, but I think I've learned from each of them. The two findings which were surprising is that in our follow-up of Romanian adoptees—these are kids who suffered profound deprivation in Romanian institutions and who were then adopted into UK families—and I wouldn't have dreamt, I have to say, of looking for autism in this group were it not for the fact that at the time we started the study I had two clinical referrals of children from that background who were said to have autism. To cut a long story short, what we found was that there was a substantial increase in what we called quasi-autistic behavior. We called it quasi-autistic because although at

age 4 the pattern was very similar to ordinary autism, by 6 it was somewhat different, and by 11, because we've done the follow-up at 11 now, was even more different. So the question then is, Is that telling you something about the cognitive abnormalities in autism, or is this an entirely different phenomenon? And I don't know what the answer to that is. I think we have to bear in mind both possibilities.

The other surprise also from the Romanian study was a substantial increase in ADHD-type problems, although again they were somewhat atypical, so that it was much more on inattention; they weren't particularly overactive, although a few of them were, and the question is again, Is that telling you something about ordinary ADHD, because neither in autism nor in ADHD does one ordinarily find many children who've been institutionalized, that's not the usual sort of background, or is it entirely different? And again hopefully the follow-up and the comparisons that we're now doing may tell us about that.

I think the other thing I've got to throw in, though, is that when we talk about environmental factors we need to be concerned that what we actually mean are nongenetic factors, and therefore one's got to take on board the possibility of either epigenetic influences of one kind or another, or development perturbations which, as it were, are feeding in. So the field is open. I don't think there's a good answer to your question, I'm afraid.

Question: Well, just on a sort of clinical level. I kept waiting for you to include in your grouping Fragile X Syndrome which seems to me to have so many of the characteristics and might be helpful in facing some of the questions you ask; we have the chromosome, we have development, we have boys, and we have psychological and other interesting sidelines to it. Would you consider it or doesn't it qualify?

Michael Rutter: Time did not allow. The Fragile X I would see actually as somewhat different, but it has certain features which are very much in common. That's to say the original claim that something like a third or even half of autistic individuals showed Fragile X is clearly wrong, and was based on quite inadequate laboratory methods as they were available at the time. And now that we've got DNA methods it's clearly less than 5 percent, and maybe a good deal less that 5 percent. But if you say what is the proportion of individuals with Fragile X who show problems, that overlap with autism then it's much larger. And so again we have this difficulty of where you draw you line, and that, as Judy Rapoport was saying, *DSM-IV* and *ICD-10* have been very useful, they're not wholly wrong, but they don't match well with certainly the boundaries of the concepts that we're now dealing with, and in some respects even with the divisions amongst them. That's one of the interesting things, and it is essentially open to research and [inaudible] will be included on the list.