

THE NEUROBIOLOGY OF DEVELOPMENTAL DISORDERS

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In recent years, technological developments have enabled the noninvasive investigation of brain anatomy and physiology in children. These advances have raised hopes of understanding "The Neurobiology of Developmental Disorders." The short-term goal of this endeavour would be to identify abnormalities in specific neurobehavioral systems that cause odd behavior, poor communication and poor school performance. Ultimately, the identification of specific abnormalities should lead to rationally targeted therapies, and even prevention.

Those goals are still distant. Even though exciting neuroscience findings invade magazines and newspapers with increasing frequency, the developmental disorders are still mysterious. A major barrier to understanding is a clinically based diagnostic classification system. There are no laboratory tests for dyslexia, specific language impairment (SLI), attention deficit hyperactivity disorder (ADHD) or autism. Dyslexia is defined on the basis of performance on reading tests, SLI by performance on language tests, and ADHD and autism by lists of clinical observations. There is a great deal of comorbidity among diagnoses and the sensitivity and specificity of most anatomical, physiological and behavioral correlates are very low.

The field is still in the data collection stage with little attempt at large scale systematization or validation of observations and procedures. Ten of the articles in this special issue adhere to this research paradigm. The remaining article stands out. In their article "Specific language impairment is not specific to language: The procedural deficit hypothesis", Ullman and Pierpont (2005, this issue) propose a theoretical account of specific language impairment (SLI) that attempts to integrate behavioral evidence with research findings from basic neuroanatomy, neurophysiology, and cognitive neuroscience. This approach represents a new way of thinking about a mystifying developmental disorder that is likely to stimulate more theoretically-focused research in future.

Section 1 contains articles that are largely phenomenological, i.e., these articles document neurobiological correlates of a particular diagnosis. The search for neurobiological correlates can be looked at as an important stage in the establishment of a syndrome, the historical precursor to identification of etiology in the study of disease. This section starts with an article on Williams

Syndrome (WS) (Jackowski and Schultz, 2005, this issue) WS is a rare but well-studied mental retardation syndrome in which many individuals have unusual verbal proficiency relative to a dramatic visual-spatial impairment. In this issue, Jackowski and Schultz confirm the original observation of Galaburda et al. (2001) that the central sulcus, a major landmark that separates motor and sensory cortex, is abnormally shallow and does not reach the midline of the hemisphere. Failure of sensori-motor cortex development could be specifically related to the visual motor deficits or it could be a more general consequence of a reduction in cortical growth (Jernigan and Bellugi, 1990). The finding is especially noteworthy because it has been documented by two independent groups, a rarity in the imaging field.

The design of the next article is also noteworthy (Guttorm et al., 2005, this issue). These investigators have searched for early markers of disability in a longitudinal family study. Such studies, although difficult and expensive, are the most appropriate way to address the interaction of nature and nurture that probably contributes to most developmental disorders. Since these disorders run in families, the collection of data before infants become probands allows unbiased prospective identification of markers that are specific for the condition, rather than part of a vulnerable genetic background. In this family study, however, the results didn't quite work out as expected. Language problems and EEG abnormalities did not distinguish the high risk and comparison families. Instead, language problems across both types of families were predicted by aspects of the neonatal EEG. As the findings were predictive for only one consonant contrast, additional studies will be required before the EEG can be used as a prospective diagnostic tool. It should be noted, however, that Molfese has also reported that neonatal EEG can predict language (in this case, reading) disability in childhood (Molfese, 2000).

The third article in the first section has a methodological focus (Eckert et al., 2005, this issue). The results of two methods of anatomical analysis are compared on magnetic resonance imaging (MRI) brain scans from the same sample of dyslexic children. One method, the manual tracing of the banks of cortical sulci visualized on a computer screen, captures the rich variability of

cortical morphology. Unfortunately, most sulci do not have clear boundaries, so measurements depend on a mixture of arbitrary criteria and subjective decisions. Although intense effort is directed at automating these procedures, it has proved extremely difficult to train computer algorithms to recognize the subtle patterns so apparent to our visual cortex. Recently, an automated technique called voxel based morphometry (VBM), has been developed. In this method the images of each experimental group are warped to a common template and the percentage of gray matter at each voxel location is reported. Eckert et al. found that both methods identify differences between the dyslexic and control groups, but the differences do not tend to be in the same locations. Manual methods appear to be superior in regions with high interindividual variability such as the inferior frontal gyrus (the location of Broca's area in the left hemisphere). The VBM method, however, has the advantage of perfect reliability, efficiency, and extensive coverage. At this stage in the development of the structural imaging field, the methods appear to provide complementary information. The major lesson from this report is that the effect of analysis technique on the findings is not trivial. Investigators should be encouraged to report findings from a series of analysis methods, a routine strategy in other forms of neurobiological research.

The last article in this section (Ors et al., 2005, this issue) uses a relatively uncommon functional imaging method – single photon emission computed tomography (SPECT), to compare children with SLI and ADHD. Children with ADHD were chosen as the comparison group because in Sweden it is considered unethical to use radioactive imaging methods in normal children. The authors make a convincing case that the children with ADHD and SLI differed on the dimension of language competence. The authors made two interesting observations. First, there was a reduction of cerebral asymmetry in the activation patterns of children with SLI, and second, subcortical regions received less blood flow. The first finding was predicted because of the well known relationship between language and the left hemisphere. The second finding is consistent with theoretical views presented by Ullman and Pierpont (2005, this issue), that SLI stems from a deficit in the cortical-subcortical circuits for procedural learning. Since there were no normal children included in the study, it is not possible to conclude that the apparent reduction in subcortical blood flow in SLI is not an increase in children with ADHD. Given prevailing cultural norms about vulnerable subjects protection, SPECT is unlikely to become a widely used technique in children. Thus, the findings in this article will require replication with the use of other techniques, such as fMRI or EEG.

The second section contains less explicitly phenomenological reports that use traditional psychological paradigms. These theoretically framed studies predicted specific functional deficits. The first article (Bishop and McArthur, 2005, this issue) investigated whether children with SLI display immature event-related brain potentials (ERPs) to auditory stimulation. An innovative aspect of this study is the application of a correlation technique that used every point in the evoked wave to compare waveform similarity. This method avoids the necessity of defining the boundaries for particular peaks in the wave. The elimination of subjective methods for waveform identification could facilitate investigation of brain development in human infants and children, where conventional peak analysis is often difficult and somewhat subjective. We encourage established ERP investigators to compare the results of application of this technique to their standard methods.

The second article (Grice et al., 2005, this issue) did not explicitly search for evidence of immaturity in children with autism. Rather, these authors predicted that the event-related potential to frontal eye gaze would be abnormal, not necessarily immature. They interpreted the result, *post hoc*, in a developmental context because the brain response to gaze direction in six year old children with autism showed evidence of an immature persistence of a differentiation that is lost in normal children.

Although the findings in the two studies described above are consistent with the idea of “developmental delay”, they raise the obvious question of why, if a disorder corresponds to a delay, there is not ultimate catch-up. One possibility is that there are critical periods for development of specific functions. If mature function is not attained by a particular age, it may never develop. These papers stress the insights that may be obtained by comparing clinical groups not just with age-matched controls but with younger typically-developing children, but they also stress the need for more longitudinal studies tracking brain-behaviour relationships over time.

Paradoxically, the third study in this section (Deutsch et al., 2005, this issue) found evidence of deviance in a study that searched for evidence of developmental delay. These authors used diffusion tensor imaging, a relatively new MRI technique that uses the directionality of water diffusion as an index of axonal size and integrity. In confirmation of a previous report (Klingberg et al., 2000), they found that axons in a particular left parietal location have less directional diffusion. Although these findings were originally interpreted as evidence of less mature connectivity, further analysis of the location of the abnormality by Deutsch et al. suggests that the fibers are actually displaced in the dyslexic children, i.e., they are

deviant, rather than delayed. It is possible that additional study of the phenomena reported by Bishop and McArthur and Grice et al. will also reveal that the less mature appearing waveforms are actually due to deviant processing by abnormally developing structural substrates. It will be interesting to see if the types of analyses pursued by Deutsch et al. reveal similar evidence of deviance in other disorders.

The last three articles in this section link electrophysiological and behavioral characteristics in autism, ADHD and dyslexia. The first study (Brown et al., 2005, this issue) analyzed the EEG power spectra of autistic children viewing ambiguous figures and found reduced power in the gamma band, a finding they interpret as evidence of impaired "binding" of stimuli. Impaired binding is a plausible unifying concept for the deficits in autism, although it is a construct that is hard to define operationally. A perplexing feature of the results is the absence of a correlation between behavioral and physiological deficits. The autistic children performed comparably to the developmentally delayed children in the control group, so the authors propose that the EEG results showed that the two groups of children were solving the problem differently. Spectral analysis is a welcome addition to the armamentarium of noninvasive neurophysiological techniques because it does not require subjective evaluations.

The second article in this section (Liotti et al., 2005, this issue) reanalyzed EEG data from a previous experiment and found that children with ADHD had less negativity associated with errors of commission in a go no go task in a location consistent with an origin in the anterior cingulate cortex. Converging evidence from many different types of investigation in animals as well as humans suggests that the anterior cingulate cortex plays a critical role in error checking, attention, and response inhibition, processes that are crucial components of the executive capacities that appear to be compromised in children with ADHD. Given the prevalence of this condition, it is surprising how few experiments have addressed the neurobiology of executive function in ADHD. Such experiments need to be designed in a developmental context, because executive function matures slowly, even in normal children. The longitudinal family design would seem especially appropriate for this population.

In the final paper of this session (Coffin et al., 2005, this issue) present striking evidence of a learning deficit in children with fetal alcohol syndrome and dyslexia. This is the only study in the special issue which describes a procedure that provides sensitive and specific evidence of a developmental disorder. Given the heterogeneity of cognitive profile in children who receive the diagnosis "dyslexia", it is remarkable that they have such a uniform profile on this behavioral test.

This successful application of procedures with a long history in animal research should stimulate other animal learning and memory experts to make the leap to human neurobiological research.

The final article is a considerable departure. (Ullman and Pierpont, 2005, this issue) propose that a core difficulty in SLI, the inability to learn and apply linguistic rules, is due, not to damage to a language specific module, but rather to a more general procedural learning system, whose attributes have been well studied in basic neuroscience experiments. These experiments have demonstrated that the neurological bases for procedural learning/habit formation are distinct from that for the declarative memory system associated with Papez Circuit and the hippocampus. Ullman and Pierpont propose that the declarative memory system is responsible for vocabulary acquisition and the learning of irregular forms of inflectional morphemes (i.e., those that violate the rule, such as past tense 'brought', 'swam' or 'went').

The use of basic neuroscience as a starting point for theory building is innovative and potentially very powerful. Theories of SLI have for some years been polarised between those who argue for a deficit in a language-learning module, and those who attempt to explain deficient language in terms of more general cognitive deficits that are not specific to language, but which play a particularly important role in language learning. Ullman and Pierpont's procedural learning account represents a clearly articulated version of the latter class of theory, which is unusual in that it sets out a view of the neurobiological deficits underlying SLI as well as the cognitive mechanisms that are implicated. Furthermore, as Thomas (2005, this issue) points out in his invited commentary on the paper, the theory is unusual in taking a developmental perspective that does not treat SLI as simply analogous to an acquired disorder in adulthood. Rather, Ullman and Pierpont take into account the possibility that in the course of neurodevelopment the brain may respond adaptively to underlying deficits and to some extent compensate for these. Thomas regards the inclusion of compensatory mechanisms as a key feature of any model of a developmental disorder, which is all too often omitted by theorists. However, he also notes that by invoking compensation as an explanatory construct, one is also sailing into uncharted waters, because we understand so little about how these mechanisms operate. His own example from a computer simulation shows that our intuitions about how compensation operates may be quite misleading.

Ullman and Pierpont's theoretical account provides a fertile source of hypotheses that will stimulate new approaches to the study of both neurobiology and behavior in SLI. It makes clear predictions not only about relationships between

linguistic and nonlinguistic deficits in affected children, but also about structure-function correlations. It also challenges us to develop truly developmental models that can explain how the brain responds when normal processes of neurodevelopment are disrupted. Computer simulations as well as behavioral and neurobiological evidence may be needed to conceptualise the ontogeny of developmental disorders adequately.

So, eleven articles that demonstrate that this is an immature but active area of research. What lessons can be gleaned? We propose six recommendations that follow our consideration of the papers in this special issue.

1. The major one, we think, is the necessity for very large samples. Multicentre collaborative studies are required to generate sufficient power for the identification of reliable associations between neurobiology and developmental disorders. Such studies are difficult, given rapid progress in imaging and genetic technology, but they remain the best strategy to counteract the slow trickle of unrepeatable findings. Small studies frequently find suggestive evidence for interesting interactions between multiple independent variables but lack the power to determine whether there is a reliable relationship. A single centre will rarely be able to marshal the resources for enough cases to design a conclusive study. Multicentre collaborations are the norm in areas such as the genetics of autism, where it has become clear that no one centre alone can contribute definitive results.

2. It will be necessary to look at brain/behaviour relationships, rather than simple group comparisons. This strategy is important because of heterogeneity within diagnostic groups and overlap between them. Neurobiological correlates may be stronger with measured behavioural variables than with a diagnosis. Including children with several developmental disorders in the same analysis may reveal relationships between neurobiological variables and cognitive or behavioral dimensions that cross diagnosis.

3. It will be necessary to combine different neurobiological methods in the same study. Such interdisciplinary research greatly increases the complexity of the design, execution and analysis of the experiments, as scientists from different research cultures don't share assumptions or vocabulary. The interdisciplinary training of young scientists may be a useful strategy here.

4. It is very important for all researchers and clinicians to be aware of the enormous individual variation that exists in brain function and structure. Averaging brains and discarding data on size and asymmetry differences seems unlikely to be a strategy that will reveal clinically useful information about single individuals, which in the end is the justification for public funding of these types of investigation.

5. In the structural field, there is insufficient evidence, at present, to accept either manual or automatic methods as the gold standard. As emphasized above, the most important goal in this area should be the replication of previous work in new samples. If results with voxel based methods prove more reliable over samples and laboratories, they will eventually replace the manual methods, even if manual measurements continue to produce occasional illuminating results. Scientific fields only progress when a critical mass of laboratories adopts similar procedures and accepts the same body of literature as a foundation. It is possible, however, that if a reliable but insensitive technique becomes "the gold standard", the field may not produce clinically useful results.

6. In studying the developmental disorders, it would seem essential to take a developmental perspective. The behavioral expression of these disorders evolves over time and changes as a function of environmental stimulation and intervention. Small individual studies frequently collapse over very large age ranges, because of the difficulty of recruiting samples of sufficient size with sufficiently homogeneous disorders.

The extraordinary results that are beginning to emerge from the Dunedin longitudinal study (Caspi et al., 2002) demonstrate the power of combining genetic and longitudinal analyses. To date such studies have not incorporated imaging in their designs because of expense and the meager evidence that imaging can be informative. It seems unlikely to us, however, that genes exert their effects on behavior without leaving traces on the structure and physiology of the brain. We urge funding agencies and investigators to consider piloting carefully designed imaging components in ongoing longitudinal studies.

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