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How neuropsychology informs our understanding of developmental disorders

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This review includes 1) an explanation of what neuropsychology is, 2) a brief history of how developmental cognitive neuroscience emerged from earlier neuropsychological approaches to understanding atypical development, 3) three recent examples that illustrate the benefits of this approach, 4) issues and challenges this approach must face, and 5) a forecast for the future of this approach. **Keywords:** Developmental cognitive neuroscience, plasticity, molecular genetics, neural network models, dyslexia, neuropsychology.

This paper will present neuropsychology as a method for understanding childhood disorders. Very simply put, neuropsychology is the study of brain–behavior relations, and developmental neuropsychology is the study of how those relations develop in both typical and atypical cases. More recently, with advances in neural network models, neuroimaging, and genetics, a field of developmental cognitive neuroscience has emerged that tests links across several levels of analysis: etiology, brain development, neuropsychology, and behavioral symptoms. So, I will argue that neuropsychology provides an important bridge across these levels and thus among the other methods described in other articles in this Annual Research Review. As it interacts with these other methods, neuropsychology itself is being transformed, and will eventually merge into the wider interdiscipline of developmental cognitive neuroscience.

This review includes 1) an explanation of what neuropsychology is, 2) a brief history of how developmental cognitive neuroscience emerged from earlier neuropsychological approaches to understanding atypical development, 3) three recent examples that illustrate the benefits of this approach, 4) issues and challenges this approach must face, and 5) a forecast for the future of this approach.

What is neuropsychology?

Since the traditional role of neuropsychology has mainly been to understand the behavioral effects of acquired lesions in adults, it has always been a clinical science that has attempted to explain behavioral symptoms in terms of theories of normal brain function. So neuropsychology illustrates well the reciprocal relation that exists between basic and clinical science. We cannot understand clinical phenomena without a theory of normal function, but clinical phenomena sometimes force revisions in our theories of normal function. The history of neuropsychology provides many noteworthy examples of both parts of this dialectic: how basic cognitive theory has been revised in response to unexpected clinical data and how advances in basic cognitive theory have changed the constructs and measures clinical neuropsychologists use to understand patients. Patient data have led to theoretical revisions in virtually every domain of cognition: vision, attention, long-term memory, short-term memory, language, and reading (McCarthy & Warrington, 1990; Shallice, 1988; Squire, 1987). In each case, the observation of a surprising set of symptoms in a patient leads to much more detailed experimental investigations, and then to revisions of basic theory. Modern cognitive science would surely be quite different without the data provided by patients with acquired lesions, yet modern neuropsychology would not exist without modern cognitive science. For instance, contemporary clinical neuropsychologists, unlike those of a few decades ago, think in terms of interacting neural systems and are much more cognizant of the brain's plasticity in the face of damage.

More recently, the application of neuropsychology to adult and child psychopathology has expanded the scope of neuropsychological theory to include domains like affective decision-making, inhibition, social cognition, imitation, emotion regulation, source-monitoring of thoughts and actions, and even the self. So there is no sharp line between neuropsychological and psychological explanations of behavior. Neuropsychology just adds the additional requirement that we try to understand psychological processes in terms of how the brain works. Hence, neuropsychologists mainly use behavioral measures in their work, but they often relate such measures to measures of brain structure or function, or even to genetic measures.

So neuropsychology, like the rest of science, is solidly committed to materialism – behavioral phenomena result from complex physical interactions in the brain – but not necessarily to reductive materialism. That is, it is unlikely that we can reduce

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phenomena like attention or memory to the behavior of individual neurons; instead, neuropsychology holds that such phenomena are an emergent property of the interactions among many neurons, and among networks of neurons. So we could say that neuropsychology is characterized by a commitment to 'emergent materialism' and is consequently committed to interdisciplinary integration.

History

As is true in psychiatry and neurology generally, child neuropsychology began as the somewhat neglected stepchild of adult neuropsychology. Although interest in individual differences in brain–behavior relations has been part of neuropsychology since its beginnings in the early 19th century (Gall & Spurzheim, 1809), for the most part, classical neuropsychology focused on the consequences of acquired lesions in adults and developed 'box and arrow' models of normal adult brain functions based on those findings. Only occasionally did these researchers consider childhood disorders. Freud (1897) wrote a monograph on cerebral palsy and Pringle-Morgan (1896) described developmental dyslexia with the term 'congenital word blindness.' Hinshelwood (1917) elaborated this construct in a monograph with the same name. Based on cases of acquired dyslexia with similar symptoms, apparently caused by damage to, or disconnection from, the left angular gyrus (e.g., Dejerine, 1891), Hinshelwood (1917) speculated that a congenital problem in the angular gyrus caused developmental dyslexia. Hinshelwood thought of the angular gyrus as a memory center for visual word forms, a concept not too different from the construct of the fusiform word area identified by modern neuroimaging, with the key difference that activity in the fusiform word area only emerges with increasing expertise in reading. Obviously, an innate center for reading per se would not make much evolutionary sense.

We can see in Hinshelwood's theory of developmental dyslexia an example of a recurring problem in the application of neuropsychology to atypical development. Theories of brain–behavior relations based on discoveries in adults with acquired lesions were applied in a wholesale fashion to children. It did not occur to these early thinkers that brain–behavior relations might *change* over the course of development, as is true for the functions of the fusiform word area.

Since this belief in invariant brain–behavior relations persisted for many decades after Hinshelwood, and is still present today in some debates today about innate brain modules, one can ask what discoveries have challenged it. Answering this question will also provide an understanding of the emergence of the field of developmental cognitive neuroscience.

A classic issue in developmental neuropsychology concerned whether the lateralization of language functions to the left hemisphere was innate or emerged as a result of a developmental process. Two developmental scientists made seminal discoveries in atypical children that strongly challenged the innate view. One of these scientists was the late Elizabeth Bates and the other was Helen Neville. Bates and colleagues (Bates et al., 2001; Bates & Roe, 2001) prospectively studied infants with unilateral brain lesions acquired before six months of age and found that early lesions to *either* hemisphere disrupted language development temporarily, but that language outcome by ages 5–7 years was within normal limits and quite similar in *both* hemisphere groups. If language lateralization to the left hemisphere were innate, then the early left hemisphere lesion group should have had both a persisting deficit and a worse outcome than the right hemisphere group.

Neville and colleagues (Neville et al., 1997) demonstrated that in congenitally deaf children a visual language (American Sign Language) comes to be represented in the left hemisphere auditory cortex, again indicating considerable plasticity in the classical language areas. These results and others lead to an emergentist perspective on brain–behavior relations, namely that the localizations of functions inferred from lesion studies in adults are the *product* of acquiring a skill and that there is room for considerable plasticity in which functions are localized where. These discoveries made it clear that we could only understand brain–behavior relations in the mature brain by understanding how they develop.

Another major impetus for the field of developmental cognitive neuroscience was a new interest in brain–behavior relations within the field of cognitive psychology. In the mid-1980s, the field of cognitive neuroscience was born, spurred in equal parts by advances in neuroimaging technology and by growing dissatisfaction among cognitive scientists about the ability of behavioral methods alone to resolve fundamental theoretical issues about underlying cognitive mechanisms – the well-known identifiability problem described by Anderson (1978).

Although there was already a rich subfield of cognitive neuropsychology which used cognitive methods to study patients with acquired brain lesions (e.g., Shallice, 1988) and which, as mentioned earlier, had produced some surprising and fundamental insights, lesion studies by themselves had inherent limitations and the vast majority of cognitive psychologists did not use this method. It was only with the advent of structural and functional neuroimaging technologies like computed topography (CT), positron emission tomography (PET), and structural and functional magnetic resonance imaging (MRI) that most cognitive psychologists became interested in the brain, leading to the rapid emergence of the field of cognitive neuroscience.

The beginnings of the field of developmental cognitive neuroscience can be traced to Lenneberg's seminal book, *Biological Foundations of Language* (1967) and subsequent work, such as the work of Bates and Neville discussed earlier, on whether the specialization of the left hemisphere for language was innate. Inspired by Lenneberg's book, considerable research in the 1970s and 1980s was conducted to test whether hemispheric specialization for language was invariant across development. Many of these studies used a relatively weak method, dichotic listening, to answer this question. Since they failed to find developmental increases in hemispheric specialization, they often accepted the innate (null) hypothesis. The classic studies of Bates and Neville using more powerful methods eventually made it clear that the answer to this fundamental question was 'no', consistent with Lenneberg's original hypothesis of progressive specialization.

There were other advances in the mid-1980s in our understanding of the development of brain–behavior relations. Some of these were contained in a special section in *Child Development* titled 'Developmental Psychology and the Neurosciences: Building a Bridge' (Crnic & Pennington, 1987). This special section contained Greenough, Black, and Wallace's (1987) now classic article on experience-dependent and experience-expectant synaptogenesis, as well as a review by the late Patricia Goldman-Rakic (1987) on her seminal work on the development and functions of the prefrontal cortex. Greenough and colleagues elegantly demonstrated that experience shapes the brain and Goldman-Rakic demonstrated that a classic developmental milestone, object permanence, depended on the development of the prefrontal cortex.

So, the field of developmental cognitive neuroscience was rapidly emerging by the mid-1980s, although its name came somewhat later. I first encountered this term in a grant that Liz Bates had written, seeking funding for her pioneering studies of children with early unilateral lesions. By adding the adjective 'developmental' to the term 'cognitive neuroscience,' Liz and other pioneers in this field who used this term, like Mark Johnson (Johnson, 1997, 2005) and Chuck Nelson (Nelson & Luciana, 2001), were doing more than saying we ought to study brain–behavior relations in children as well as adults. Instead, this addition signaled a bold theoretical claim, that cognitive neuroscience would be fundamentally incomplete without an understanding of how brain–behavior relations develop. In other words, we cannot understand how the mature brain functions without understanding how it develops. This claim rested in part on dramatic advances in developmental neurobiology made by Hubel and Wiesel (1963), Hubel, Wiesel, and Stryker (1977), Greenough (Greenough et al., 1987), Shatz (1992) and others. These advances made it clear that plasticity was an intrinsic and necessary property of normal brain development, and that instead of being 'hardwired' at birth, neural circuits (and the mental structures they mediate) emerge as a result of interactions among neurons, whose activity is initially endogenous and then increasingly responsive to environmental stimulation.

So mental structures are a product of probabilistic epigenesis (Gottlieb, 1992) or neural constructivism (Quartz & Sejnowski, 1997). Hence, Piaget's emergentist theory about the ontogeny of a child's concepts and mental operations could be potentially grounded in the materialist details of interactions among neurons in neural networks. Hence, the cognitive architecture of a 'typical' adult is the product of a developmental process, just as is cognitive devolution in aging, and we cannot full understand that cognitive architecture without understanding how it developed (and keeps developing, because plasticity also characterizes the adult brain).

Another important scientific breakthrough contributed to this perspective, namely the development of connectionist or neural network models (O'Reilly & Munakata, 2000; Rumelhart & McClelland, 1986). These networks modeled the emergence of mental structures from the interactions of artificial neurons exposed to a particular learning history, and became an extremely powerful tool for studying typical and atypical development.

The fact that a given individual's cognitive architecture is a product of their own developmental and learning history leads to an important corollary: the study of individual differences will provide important insights about what is constrained and what can vary in brain and behavior development. Atypical development provides an important test of the universality of developmental processes and sequences. As Neville's work with the congenitally deaf demonstrated, differences in experience will change brain development and the localization of functions. We now have many more examples of this phenomenon, from musicians, blind readers of Braille, and others (e.g., Galaburda & Pascual-Leone, 2003). These examples make one wonder how many individuals actually have typical development or whether typical development is more of an average across diverse developmental trajectories.

But individual differences also arise from genetic differences and the interaction of genes and environment. So, another important component of developmental cognitive neuroscience is behavioral and molecular genetics. We are beginning to understand how the typical chemistry and wiring of the brain is influenced by genes, how genetic variations alter this chemistry and wiring, and how these genetic variations interact with environmental factors to alter developmental trajectories (Rutter, 2006). We now turn to particular examples of the power of the developmental cognitive neuroscience approach.

Examples of a multilevel understanding of atypical development

There are now several examples of the successful application of a developmental cognitive neuroscience approach. In each of these examples, we can now trace a causal path from etiology to brain development to cognition and finally to an individual's conscious experience. We consider three examples here: children with infantile cataracts, early treated phenylketonuria (PKU), and developmental dyslexia. Children with each condition experience a somewhat different world as a result of early changes in brain development. In the case of infantile cataracts, the effect on brain development is environmentally mediated, whereas in dyslexia and early treated PKU it is genetically mediated. In the cases of early treated PKU and infantile cataracts, the analysis began with a known medical syndrome and worked 'forward' to behavior. In contrast, in the case of developmental dyslexia, the analysis began with behavior and worked 'backwards' to the brain and to genes. A brief description of each of these examples follows.

Unless removed early, infantile (but not adult) cataracts cause blindness in the affected eye, thus disrupting the binocular visual input necessary for the formation of ocular dominance columns, which segregate visual input from each eye in primary visual cortex (Shatz, 1992). A similar problem can result from early misalignment of the eyes, termed esotropia and colloquially known as 'cross-eyes' (Held, 1985). Either condition disrupts the segregation of visual input from each eye to the brain. This segregation of input is necessary for the brain to detect when each eye is fixating on the same object in the world and to compute information about depth in the visual scene. Neural network models of typical and atypical development of ocular dominance columns (Miller, Keller, & Stryker, 1989) and of stereopsis (Churchland, 1995) have been developed. In sum, we have a fairly complete account in neural terms of how an alteration in early environmental input changes brain development and the computations performed by neural networks to lead to a change in conscious experience – loss of three-dimensional vision.

In the second example, early treated PKU, it has become clear that even mild elevations of phenylalanine levels lead to a dopamine depletion syndrome that differentially affects prefrontal and retinal neurons, leading to deficits in working memory and contrast sensitivity (Diamond, Prevor, Callender, & Druin, 1997; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990). PKU is a classic inherited metabolic disorder due to a single autosomal recessive mutation of the gene that codes for the enzyme phenylalanine hydroxylase. Without this enzyme, the child cannot convert phenylalanine to tyrosine, the necessary precursor for dopamine synthesis. Both the retina and the prefrontal cortex are particularly sensitive to dopamine depletion, and so their function is differentially disrupted by such depletion. As a result, a child with early treated PKU has less control of their thoughts and less visual acuity.

A fairly mature cognitive science of reading facilitated neuropsychological studies of the cognitive phenotype in dyslexia (Pennington, McGrath, & Smith, in press). Elucidation of this cognitive phenotype then enabled studies at other levels of analysis, including molecular genetics, brain development, neural network modeling, neuroimaging, and treatment. The etiology of dyslexia fits a general multifactorial model in which genetic and environmental risk and protective factors combine to produce a disorder defined by reading and spelling problems in some individuals. Recently, several candidate genes for dyslexia have been identified and ribonucleic acid (RNA) interference studies in animals have demonstrated that these genes are important for neuronal migration and axon guidance (Pennington et al., in press). So risk alleles for dyslexia appear to change brain development by changing how connections among neurons develop, a finding that is consistent with earlier neuropathology studies by Galaburda and colleagues (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Functional neuroimaging studies indicate that reading requires integration among several brain centers, including posterior and anterior portions of language cortex and the fusiform word area. This integration depends crucially on connections both within and between these brain centers, so the early changes in neuronal connectivity produced by these risk alleles likely make it harder to integrate the brain centers required for reading.

Of course, these brief sketches gloss over many things that we do not yet understand. But I think they demonstrate the potential power of a developmental cognitive neuroscience approach.

Issues and challenges

Because the mapping between brain and behavior is complex and changes with development, some earlier uses of neuropsychology to understand behavioral disorders are undoubtedly too simple. In this section, we consider two examples: single vs. multiple deficits and endophenotypes.

It is important to point out the key assumption underlying the neuropsychological approach, which might be called the cognitive or psychological premise (see Morton & Frith, 1995). What this premise asserts is that explanations of normal or abnormal behavior, such as skilled or dyslexic reading, framed in terms of underlying psychological or cognitive constructs are more parsimonious than either an inventory of all the correlated behaviors or a reduction to neurophysiology. If a disorder like dyslexia

has a single cognitive cause, such as a deficit in phonological representations, then this is a powerful premise indeed.

But the question is how well does the psychological premise hold up when we start to view the causes of typical or atypical behavior as being multifactorial at the cognitive or psychological level (Bishop & Snowling, 2004). It is becoming increasingly clear that single cognitive deficit models of developmental disorders, like dyslexia, attention deficit/hyperactivity disorder (ADHD), language impairment, or autism, do not work. Instead these syndromes appear to arise from *combinations* of cognitive deficits (Pennington, 2006). Moreover, such disorders only rarely occur in isolation and they often share cognitive deficits. This comorbidity is an important impetus for a multiple cognitive deficit model of developmental disorders (Pennington, Willcutt, & Rhee, 2005). While I do not advocate abandoning the psychological premise, theoretical work is needed on how the interaction among cognitive deficits leads to clusters of symptoms that define clinical syndromes.

Now we turn to our second example, the concept of an endophenotype. Somewhat earlier in the field of developmental cognitive neuroscience it was hoped that 'marker' tasks would simplify the task of studying brain–behavior relations in children or immature animals. If a given task was sensitive to dysfunction of a given brain structure in adults, then that task or a suitable variant could be used as a marker for function or dysfunction of that brain structure in children. But there are three fallacies in this logic. One is that we have already solved the localization problem in adults and that the solution is simple, i.e., there is a straightforward mapping between behavioral tasks and brain structures. Neuroimaging and other results have helped us discard that fallacy, although it still persists (see Van Orden, Pennington, & Stone, 2001 for a discussion). The mapping between a task, even a task component, and brain structures is complex. The second fallacy is that brain behavior–relations are invariant across development. We now know this is not the case for language, vision, attention, and likely memory. The third fallacy is that the causal arrow is unidirectional, from brain to behavior, instead of bidirectional (see Oliver, Johnson, Karmiloff-Smith, & Pennington, 2000).

A newer incarnation of marker tasks can be found in recent research on psychiatric genetics in the concept of endophenotypes. The hope is that by finding simpler behavioral phenotypes that are associated and coheritable with a complex behavioral disorder, we will make it easier to find some of the genes that contribute to the complex behavioral disorder. Although this strategy has shown some promise, we must be careful to not oversimplify the mapping between genes and endophenotypes. Just as there are *not* genes for schizophrenia, there are *not* genes for endophenotypes of schizophrenia. Instead, there are genetic variants that increase the risk for the development of schizophrenia and it is possible (but not yet proven) that a smaller set of these genes increases the risk for the development of an endophenotype of schizophrenia. Especially when the endophenotypes are behavioral, they face some of the same complexities faced by marker tasks. For instance, deficits on certain eye movement tasks, like smooth pursuit, are accepted as endophenotypes in schizophrenia, but the mapping of smooth pursuit on to the brain and especially onto the genome is likely very complex (Flint & Munafo, 2007). While it is conceivable that a single risk allele might disrupt a single receptor type and this might lead to a deficit in smooth pursuit, there will be many other ways to disrupt smooth pursuit, as well as or protective factors that lead some individuals with the risk allele to have normal smooth pursuit.

In summary, the mapping between brain and behavior is complex, bi-directional, and changes with development. The same is even more true for the mapping between genes and behavior. Although behavior does not change deoxyribonucleic acid (DNA) sequences, it does affect gene expression. Most developmental scientists understand the complexities in localizing behaviors or deficits. Their sophistication in analyzing behavior and interpreting relations with other levels of biological analysis will be crucial as our capacity for finding genes and brain structures that influence complex behaviors increases.

The future

As the field of developmental science increasingly adapts neuroscience methods and collaborates with neuroscience and genetic researchers, it is important to not forget what behavioral scientists bring to these endeavors. To put it bluntly, scientists in these other fields need our expertise as much as we need theirs. Imaging or genetic studies of a behavioral phenotype depend crucially on the understanding of the behavioral tasks involved and the investigators' sophistication about developmental theory. It is not hard to think of examples of multilevel research where the significance of a behavioral task was oversimplified or reified. The Morris water maze is not simply a marker for hippocampal function, nor is the Wisconsin Card Sorting Test a simple marker for prefrontal function. So multilevel research and interdisciplinary collaborations depend crucially on sophisticated cognitive and behavioral analysis. Just as neuropsychologists are not trained in the nuances of genetics, geneticists are not trained in the nuances of interpreting neuropsychological data.

So neuropsychology is merging into the field of developmental cognitive neuroscience, and as it does so, it is being transformed. Many of the core assumptions held by neuropsychologists just 20 years ago have been overturned and a new

neuroconstructivist theoretical framework (e.g., Mareschal et al., 2007) is replacing them. The classical assumptions of fixed localization of function and a maturational view of development are being replaced with a theory of interactive specialization.

Perhaps the most exciting prospect for the future of neuropsychology and developmental cognitive neuroscience is the potential for an even wider interdisciplinary integration. The incorporation of molecular genetics into the field of developmental cognitive neuroscience provides a key link to the fields of developmental neurobiology (e.g., Sanes, Reh, & Harris, 2006) and evolutionary developmental biology – shortened as 'evo devo' – (Carroll, 2005). Both fields are concerned with essentially the same fundamental question as developmental psychology, which is how do new forms emerge from simpler ones. Developmental neurobiology is concerned with how the form of the nervous system emerges in ontogeny and evo devo is concerned with how new forms emerge in evolution. Evo devo has provided the profound insight that the widely different forms found across animals are not produced by species-specific genetic architectures but by variations in the timing of expression of an ancient and generic set of 'tool kit' genes. So what evolved is developmental differences in the sequence and timing of expression of these tool kit genes. In other words, evolution works by 'tweaking' development, and these tweaks lead to an incredible variety of life forms. Evo devo makes it clear why there is considerable genetic homology across species, and why animal models can be so valuable for understanding human developmental neurobiology.

So, the seemingly innocuous addition of the word 'developmental' to the new interdiscipline of cognitive neuroscience has profound implications. This addition has the potential to integrate our field with virtually all of biology and points toward a truly interdisciplinary developmental science that will likely find common answers to the question of how new forms arise across various levels of analysis.

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Key points

- The field of neuropsychology, which attempts to understand brain–behavior relations, had long assumed these relations are innate and static.
- But accounting for typical and atypical behavioral development has made us understand that brain–behavior relations are plastic and change with development.
- An interdisciplinary field of developmental cognitive neuroscience has emerged that uses multiple methods, including molecular genetics, neuroimaging, neural network models, and behavioral experiments, to understand the development of brain–behavior relations.
- This field is now producing multilevel explanations of atypical development, such as the loss of stereoscopic vision in children with infantile cataracts, executive deficits in children with early treated phenylketonuria, and how alterations in genes that control neuronal migration lead to dyslexia.
- The field of developmental cognitive neuroscience holds the promise of an even wider intergration, such as with the fields of developmental and evolutionary biology.

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