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Designing studies to investigate the relationships between genes, environments, and developmental language disorders

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ABSTRACT
This paper focuses on designing studies that will compare children with developmental language disorders (DLD) drawn from several syndromes in which there are primary impairments in the acquisition of language. This kind of research can be used to address four key questions: (a) What are the developing language phenotypes that characterize specific disorders? (b) What factors are key precursors and predictors of language acquisition in DLD? (c) What are the genes that contribute to DLD in different syndromes? (d) What environmental factors influence the trajectories of language development in DLD? Several design issues are discussed including an overall study design, subject selection and recruitment, matching and comparisons across groups, and methodologies. A number of important challenges to the design and implementation of these kinds of studies are presented in the final section of the paper.

For almost all children the acquisition of language is a remarkable, rapid, and joyful experience accomplished with no formal teaching by either parents or professional educators. Textbooks note the ease with which children reach the most significant milestones, including the rapid expansion of a rich and varied lexicon, steady growth in utterance length reflecting advances in grammatical and morphological complexity, as well as developmental changes in conversational and other discourse skills (e.g., Gleason, 2000; Hoff–Ginsberg, 2000). Studies demonstrate remarkable similarity across children and languages in the timing of the onset and mastery of these milestones, as well as in the rates of developmental change within and across these components of language (e.g., Tomasello & Bates, 2001). By the end of the preschool years children have acquired a mature linguistic system, though developments in vocabulary and discourse skills continue throughout middle childhood and beyond. In sum, a good deal is known about normal patterns of language acquisition, including the environmental and cultural factors that influence certain aspects of the developmental process (e.g., Massey, 1996; Ninio & Snow, 1996). At the same time, although there is strong evidence for the

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role of genetic factors in language acquisition, the study of normal populations has not yet led to the identification of specific language genes (Plomin & Dale, 2000; Spinath, Price, Dale, & Plomin, 2004). It is clear, however, that the timing and process of language acquisition involve the complex interplay of both genetic and environmental influences.

For a small number of children, language acquisition does not proceed with ease. Developmental language disorders (DLDs) occur in the majority of children with neurodevelopmental disorders, particularly those resulting from genetic abnormalities such as Down syndrome (Chapman & Hesketh, 2001) or fragile X syndrome (Abbeduto & Hagerman, 1997) or from complex inherited syndromes such as autism spectrum disorders (Lord & Paul, 1997). Deficits in acquiring language are also the defining symptoms in specific language impairment (SLI), a complex behavioral disorder diagnosed by excluding the presence of other disorders or mental retardation that might explain the core language problems (Leonard, 1998; Rice, 1999). In contrast to highly predictable patterns of language development that are found among typically developing children, there is significant variability among children with DLD both within and across different populations (Bates, 2004).

Over the past several decades many studies have been conducted investigating language impairment in different populations. This body of research highlights the parallels and differences within and across different aspects of language acquisition, as well as some of the critical factors that are related to specific deficits in language in various populations that have been studied, such as the role of auditory working memory in the grammatical deficits found in Down syndrome (Jarrold & Baddeley, 2001) or the role of theory of mind in understanding the pragmatic deficits in autism (Tager–Flusberg, 2000). Nevertheless, there are still very few longitudinal studies tracing developmental pathways in key populations that suffer from DLD. Such research is important on both theoretical and applied grounds. At the theoretical level, there is the real promise that such investigations will lead to the discovery of specific genes that contribute to the neurocognitive underpinnings of language acquisition, as well as how those genes interact with particular environmental factors in shaping the course of language development. At the applied level, detailed longitudinal studies will promote new intervention techniques and programs to enhance language and communication skills in children with specific patterns of DLD targeted at particular developmental stages. In this paper we focus on key issues regarding the design of research investigations that address several questions that were identified at the 2003 Merrill Conference (see also McCardle, Freund, & Cooper, 2005).

RESEARCH QUESTIONS

Comprehensive research programs focusing on DLD in different populations, including Down syndrome, Williams syndrome, fragile X syndrome, autism, and SLI, are needed to answer the following questions.

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What are the developing language phenotypes that characterize specific disorders?

This question concerns the natural history of language development, with particular emphasis on the timing of acquisition. This includes the onset (e.g., when children begin to babble, comprehend, or produce words or phrases), rates and developmental trajectories for specific components of language (e.g., vocabulary, syntax, morphology), and asymptotes or end points (Rice, 2004). Studies of developing phenotypes may illuminate unusual changes in developmental trajectories, such as the regression patterns that have been identified in autism (Lord & Paul, 1997), and will reveal distinct patterns, profiles, and dissociations among language components at different developmental stages. One major goal is to compare developing language phenotypes across the various syndromes of interest.

What factors are key precursors and predictors of language acquisition in DLDs?

Language is a complex domain-specific system that interfaces with other cognitive systems. The intersection between the various components of language and related cognitive mechanisms is likely to change over time. Moreover, developmental trajectories in different populations are likely to be linked to different factors that are important in the process of acquiring language. Examples of such factors include oral–motor skills, vocal repertoire, imitation, gesture, and social engagement, all of which emerge during the first year of life in typically developing children. Furthermore, general cognitive factors including IQ and auditory memory influence the rate of language development, at least in some children with neurodevelopmental disorders. Together, these factors may be considered important ingredients of language acquisition but we know little about which of these predict language impairments in specific syndromes at which developmental stages. Research that addresses these issues is likely to lead to the ability to identify and thereby intervene with children at risk for DLD at much earlier ages than we currently can do.

What are the genes that contribute to DLD in different syndromes?

Genes influence language acquisition through their effect on the developing neural systems that underlie language and language-related processing mechanisms (see Fisher, 2005, on how the *FOXP2* gene contributes to language-related impairments in the KE family). In fragile X syndrome we have the opportunity to identify the effects of a known specific protein (fragile X mental retardation protein; Jin et al., 2004), on the developing brain and its influence on language acquisition. In other syndromes such as Down syndrome we have yet to discover which gene or genes on chromosome 21 contribute to the language or language-related impairments and to the developmental timing of cognitive systems. For complex disorders such as autism or SLI we need to continue the search for the specific genetic mutations that confer risk for DLD using a variety of methodological approaches from behavior to molecular genetic studies. Ultimately, these investigations will provide clues to

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the specific functions of these genes and address the question of whether different genes lead to similar or distinct atypical patterns of brain development associated with DLD.

What environmental factors influence the trajectories of language development in DLD?

Genes interact with environmental factors from the earliest stages of development. Studies of language acquisition in children with DLD can illuminate these interactions, especially the environmental factors that we know are important in the postnatal period, including cultural and socioeconomic factors, parent–child interaction, as well as targeted interventions (Thorpe, Rutter, & Greenwood, 2003). We do not yet understand the mechanisms that mediate how such environmental factors may influence developmental patterns and trajectories, yet it is likely that their influence is multifaceted, ranging from the input available to the child, the optimal contexts for acquisition, and the environmental influences on the learning process itself. More broadly, we are also interested in the interactional effects between the child and the environment, thus going beyond how environments help to shape development, to how children, in reciprocal ways, shape the environments in which they are acquiring language.

DESIGNING RESEARCH INVESTIGATIONS

It is clear that no single study can adequately address this range of questions and issues concerning DLD. Instead, we envision a series of interlocking research programs that encompass different populations, age ranges, and methodologies. In order to address the key questions concerning developmental phenotypes, as well as predictors of DLD, *prospective longitudinal studies* are needed, ideally beginning early in infancy. In this way we can capture the important precursors associated with DLD in different syndromes, and the onset of basic language milestones, without depending on retrospective parental report. This would not be difficult for studying language acquisition in the basic genetic syndromes, such as Down syndrome, which are identifiable at birth or even prenatally. In contrast, given that autism and SLI are not diagnosed until the toddler or preschool years, studies generally could not begin until after the earliest milestones have been missed, thus losing the opportunity to directly investigate the critical period before and during the onset of language. To circumvent this challenge, one can implement research programs that focus on high-risk infants, specifically younger siblings of children identified with these disorders (e.g., Benasich & Tallal, 2002; Zwaigenbaum, 2004). To cover the full age range from onset (or even earlier) to the end point (which may not be reached in some neurodevelopmental disorders until well into adolescence), would take many years to complete with a straightforward longitudinal design; instead, a cross-sequential accelerated longitudinal design could be implemented in which several samples, each beginning at a different age, would be enrolled.

In recent years, powerful new multivariate statistical growth-modeling methods have been used in the analysis of longitudinal data. These statistical methods are

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especially well suited for analyzing developmental trajectories, both within and across populations. Variation in rates of development, the type of growth curve, and predictors of development can be identified for different aspects of language acquisition, as demonstrated for children with SLI in the recent work of Rice (2003).

Designing longitudinal studies involves numerous important decisions regarding subject selection, group comparisons, methods, and measures. We briefly review some key issues that need to be considered for studying the acquisition of language and defining language impairments in DLD.

Subject selection and recruitment

For each population, both inclusionary (or defining) and exclusionary criteria need to be clearly specified. For genetic syndromes such as Down syndrome or fragile X syndrome, clinical identification is no longer sufficient. Genetic testing must be conducted to confirm the status of each individual participant. For complex disorders that are diagnosed solely on the basis of behavioral symptoms, including both autism and SLI, the use of reliable, agreed upon diagnostic instruments is crucial, which is confirmed by expert clinical impression. In autism, these include the Autism Diagnostic Interview—Revised (Lord, Rutter, & LeCouteur, 1994) and the Autism Diagnostic Observation Schedule (Lord et al., 2000). There is less agreement in the SLI research community about how to define this disorder, especially in children at different ages. Although some clinical markers for SLI have been identified (see Tager–Flusberg & Cooper, 1999), including impaired performance on nonword repetition and difficulties marking grammatical tense, standardized tests for these constructs are only available for children over the age of 3. Furthermore, SLI is defined in terms of language abilities that are below age expectations, but there is still no consensus regarding how this should be quantified on standardized tests (e.g., 1 standard deviation below the mean, 1.5 standard deviations, etc.) or which components of language must be impaired in order to qualify as SLI.

Which exclusionary criteria for participants should be implemented in research programs on DLD? Across all groups we need to consider hearing loss and nonnative language background as potential exclusionary criteria because we know that these variables can significantly affect the timing and course of language acquisition, independent of DLD. Some also argue that children with a history of seizures, a marker for more compromised brain pathology, should also be excluded from these kinds of studies. The definition of SLI explicitly involves exclusionary criteria, which include hearing loss, mental retardation, significant neurological impairment, and autism or other psychopathology. However, few studies apply rigorous objective standards for ensuring that children objectively meet all these criteria. For autism research, it would be important to exclude nonidiopathic autism, that is, autism symptoms that are secondary to some other genetic disorder (e.g., tuberous sclerosis, fragile X syndrome, etc.) confirmed with genetic testing. Moreover, given that there is some overlap between autism and SLI (e.g., Bishop, 2000; Tager–Flusberg, 2004), this suggests that some clear criteria

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for defining and distinguishing between these heterogeneous complex disorders are needed.

It is typical for research investigations of DLD to recruit samples from clinics or other, similar institutions, such as special schools serving these populations. Although it is clearly expedient to use clinically referred samples, they potentially introduce a significant bias toward those children who have more severe language impairments, or greater access to services, and perhaps this recruitment approach introduces a gender bias to the sample. Some attention needs to be given to incorporating a wider range of methods for ascertaining subjects in order to obtain more representative samples.

Comparisons across groups

In any research that compares the acquisition language across different groups of children the question about how to match the groups is raised. Mervis and colleagues have summarized numerous concerns about research that attempts to match groups on a variety of control variables (Mervis, 2004; Mervis & Klein–Tasman, 2004; Mervis & Robinson, 1999). There are several significant differences among populations with DLD, such as IQ distributions, timing of diagnosis, and the presence of co-occurring symptoms, all of which indicate that only limited matching procedures should be implemented. The key variables that need to be considered include age, socioeconomic status, and gender, variables that influence language acquisition across all populations. By holding age constant we can directly compare developing language phenotypes across groups. In this way, we can address the question of whether age of onset influences developmental trajectories in the same or different ways across populations. Because socioeconomic factors, especially maternal education (cf. Dollaghan et al., 1999; Hart & Risley, 1995), are known to influence certain aspects of language development, it would be important to ensure that the groups were well matched on this variable. Similarly, gender also influences language acquisition (Bauer, Goldfield, & Reznick, 2002; Gleason & Ely, 2002), although one complication with matching on gender is that some syndromes with DLD are more prevalent in males than females, including fragile X syndrome, autism, and probably SLI.

Instead of matching groups, group comparisons can be made on developmental profiles and patterns of language skills within and across different components of language. Multivariate statistical approaches can be used to investigate the influence of different variables, including IQ, auditory working memory, imitation, and so forth on language acquisition in the various populations with DLD. In this way we may discover, for example, whether IQ is an important predictor of language acquisition for some populations but not for others at different developmental stages (cf. Rice et al., in press).

Methods and measures

Language acquisition can be studied using a broad range of methodologies, from parent report to novel experimental paradigms. Different methods may be best

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suited to collect data on receptive and expressive abilities at different ages as well as to capture developments in different domains in language, for example vocabulary and pragmatic skills. The most common methods that have been used across both typically developing and language-impaired children include: parent report (for the earliest stages of language development, especially the one-word stage); naturalistic observational methods; collecting language samples during conversational interactions; standardized language assessments; and experimental probes and learning or training paradigms. It is even possible to explore individual differences in developmental trajectories within the context of language intervention studies (Warren, 2004).

A comprehensive research program on language development should include, where possible, multiple measures for each key construct. The issue of measurement for research on DLD is covered in detail in this issue's paper by Mervis and Robinson (2005), including a discussion of some of the domains for which new measurement development is crucially needed. One issue that until recently received relatively little attention in language research is the inclusion of measures that are heritable. For research programs designed to investigate the interaction of genetic and environmental factors, it is crucial to include language measures with known heritability estimates.

In order to reach beyond the investigation of developing language phenotypes we need to consider the methods and measures needed for the collection of data related to the major putative precursors and predictors of language development in different syndromes. Again, it is desirable to have more than one measure for each construct incorporating parental report, direct observational, and standardized assessments, where possible. This goal needs to be tempered with a realistic evaluation of the amount of time a child and his or her family can reasonably be asked to contribute to a research program.

To address genetic studies, DNA samples from both the child and the parents will be needed. Alternatives to the collection of blood samples, which can be painful and frightening to young children, should be considered, for example using buccal swabs or saliva to obtain DNA from individuals not willing or able to give blood. Questions regarding the language phenotypes in family members of children with DLD can be addressed by collecting data from parents, siblings, and other relatives, although it is rarely possible to use the same measures of language or language-related cognitive abilities across a wide age range spanning from young children to adults.

CHALLENGES

We have presented here an ideal, rich, long-term research program that will ultimately lead to genuine advances in our understanding of DLD. No single research group or site can undertake this program; rather it needs to involve a multidisciplinary team of scientists drawn from many laboratories. Many questions remain regarding the design of this research program; indeed, many empirical challenges need to be considered. In this final section we briefly highlight some of these challenges.

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Sample size

How many children in each population would be needed, especially given the wide variability in the language phenotypes in disorders such as autism or fragile X syndrome? Given that many of these syndromes are quite rare it may be difficult for a single site to enroll all the participants needed.

Diagnostic overlap

As noted earlier there is overlap between some of the populations of greatest interest including autism and SLI, or autism and fragile X syndrome. How can we address this issue of overlap? One approach, suggested above, is to draw clear-cut definitions for each disorder, ensuring the absence of any overlap. Another equally valuable approach would be to *include* children who seem to fall between syndrome boundaries, thus allowing one to compare the developing phenotypes of children that fall on a continuum rather than in mutually exclusive diagnostic categories (cf. Bishop, 2000).

Sampling times and settings

How often should data be collected from the children? We know that developmental changes in language generally occur more rapidly during the early years, suggesting that at least from infancy to the early school years a minimum of four visits each year might be needed to capture the major stages of language acquisition. In later years this schedule could be reduced. Under what conditions should naturalistic observational data be collected? Choices include, for example, home, lab, and school settings; with a parent, other adult, or peer social partner; or in play, structured activities, or a conversational setting with no supporting materials. Decisions on these variables depend in part on the child's overall developmental level and stage in language acquisition.

Multisite investigations

We have already noted that the breadth of this research program we envision will require multiple sites to be involved in data collection, coding and analysis, and interpretation. How will reliability for diagnosis and measurement be maintained across sites? If interventions are incorporated as part of the investigation, issues regarding fidelity to treatment protocols must also be considered. Plans for coordinating and integrating data collected across sites must be prepared before the first participants are enrolled.

Language

Most research on DLD has focused on children acquiring standard, nondialect forms of English. However, we know from the few crosslinguistic investigations that have been conducted that DLD is manifest in different ways across different languages (e.g., Leonard, 2000). Ultimately, we will need to replicate research

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programs across a range of languages in order to meet the clinical needs of children with DLD around the world.

Numbers of measures

Investigating language acquisition in a comprehensive way requires the inclusion of many measures covering a significant number of constructs (including both language and more general cognitive domains). How can we keep the number of measures to a reasonable level so that data collection is both feasible and not overly burdensome to children and their families?

Interventions

Most, if not all, children enrolled in a language research program focusing on DLD will also be receiving some treatment that itself will influence the data we collect on developmental trajectories. Although this cannot be avoided, some consideration must be given to how to document and keep track of the children's interventions and how to incorporate these data into our analyses and interpretation of the major findings.

Parent measures and family history

The interest in both genetic and environmental factors in the process of language acquisition in children with DLD raises questions about collecting relevant data from family members. As noted earlier, direct assessment of language skills in parents and other relatives is important, yet language measures are not comparable across the lifespan and there is no consensus about how to document language impairment in adults. Family history information is especially important for genetic studies, so some thought must be given to how this might be collected in a reliable and valid form (e.g., Piven, 1999).

Brain mechanisms

How feasible is it to include young children in studies of brain structure and function? Because our ultimate goal is to link genes and environments to in-depth investigations of the developing language phenotypes found across syndromes with DLD, our ideal research program would incorporate both behavioral and neuroimaging measures of the phenotypes. In this paper we have focused primarily on the behavioral aspects of the phenotype; however, see Phillips (2005) and Müller (2005) in this issue for more detail concerning neuroimaging studies of children with DLD.

SUMMARY

We have outlined here a highly ambitious and exciting program of research that, despite the enormous challenges in implementation, will significantly advance our understanding of language acquisition and language impairments in children

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with DLD drawn from different neurodevelopmental disorders. The opportunity to investigate developing language phenotypes in individuals with genetically based disorders offers the unique promise of uncovering links between specific genes, neural development, and language acquisition.

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