

NICHD Vision Workshop on Cognition Workshop

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I. INTRODUCTION/BACKGROUND

Cognition is central to how we experience and affect the world. Key elements of cognition include perception, attention, learning and memory, judgment and decision making, reasoning, language, and executive functioning. The development of cognition requires the orchestration of genetically guided biological substrates interacting with the environment, and corresponds with remarkable changes in brain structure and function. Although much of cognition is shared with non-human species, its extended and remarkable development in humans is the feature that most distinguishes us from all other species. Unfortunately, cognitive development does not always proceed to its desired end state. When disorders in cognitive development occur, the consequences can range from mild to profoundly debilitating. Although we know much more about the development of cognition than we did a decade ago, at best we have made a very small scratch on a very large surface.

This workshop brought together over fifty experts from a wide range of disciplines relevant to understanding cognition, including epidemiologists, developmental psychologists, cognitive scientists, cognitive neuroscientists, developmental neurobiologists, geneticists and clinicians from a variety of perspectives (psychiatry, psychology, education, pediatrics, neurology) to identify scientific opportunities over the next decade that will have the greatest impact on research and practice in the domain of cognition. The focus of the workshop was on cognition and the development of cognition, from conception through adulthood, highlighting the dynamic nature of change during childhood that must be a cornerstone for any research on cognition during this period. It is conditioned on a view that optimizing developmental outcomes for children involves a range of research that begins with theory and the mapping of typical developmental trajectories in multiple domains of inquiry; the use of this research to develop models of typical and atypical development that integrate mechanisms derived across domains involving genes, brain, and environment; and the development of informative strategies to improve function and outcomes. Research perspectives encompassed the areas of typical and atypical development, human and animal studies, research into phenomenology, underlying behavioral and neurobiological mechanisms, pathogenesis; screening, assessment, prevention and intervention; and building capacity of both the research work force, through training and new approaches to collaboration and advancing resources available for research.

To facilitate the discussion in key areas likely to have the greatest impact, the workshop began with five plenary sessions. Charles Nelson, Ph.D., reviewed issues underlying research on typical and atypical cognitive development, emphasizing the role of both genes and experience, along with trajectories punctuated by sensitive periods for acquisition. Dr. Nelson emphasized the importance of understanding typical development to provide a roadmap that can be used to better understand examples of atypical development. Matthew State, M.D., Ph.D., provided an overview of recent and ongoing technological advances in the field of genetics, and their application to understanding the genetic bases of cognitive disorders. Dr. State pointed to the particular challenge of sorting through the tremendous amounts of information becoming available on the human genome for both research as well as the potential for incorporation into the clinical care of individuals. The importance and potential contributions from the perspective of basic developmental neurobiology were discussed by Alcino Silva, Ph.D., who described

progress in understanding some of the key molecular and cellular underpinnings of single gene disorders associated with deficits in the development of cognition, and promising targeted pharmacologic treatments for these conditions based on knowledge of the underlying molecular biology. Dr Silva echoed the comments of Dr. Nelson in pointing out the need to understand sensitive periods in the development of brain plasticity and response to the environment. The rapidly developing capabilities of tools for characterizing brain structure and function was the topic of a presentation by Beatriz Luna, Ph.D., along with the role of these tools in unraveling the brain systems underlying cognition and cognitive disorders of development. Dr. Luna emphasized integration of imaging, genetic, and behavioral data. Finally, Jack Fletcher, Ph.D. provided an overview of behavioral interventions for disorders of cognition, identifying characteristics of effective interventions. Dr. Fletcher emphasized the importance of incorporating multiple levels of analysis when examining the effects of interventions, and emphasized that many cognitive disorders represent performance at the tails of continuously distributed variables rather than distinct entities.

Participants met in several small group sessions over the course of the day and a half meeting to explore the following questions: (1) What are the most promising scientific opportunities of the next decade relevant to cognition? (2) What basic, clinical, and translational research questions must first be addressed to exploit these opportunities? (3) How would answering the questions affect public and global health and advance the NICHD mission? (4) What research tools, methods, or approaches should be developed to realize these scientific and public health opportunities? (5) And finally, what innovative training and other workforce development activities should be pursued? The emphasis of the meeting was in generating ideas from the participants and no pre-determined discussion topics were proposed. Six small groups were composed of members across the spectrum of disciplines attending the meeting.

If we were to identify a single theme that emerged from the meeting, it would be the theme of integration. Most of the small group and large group discussion touched on integration in various forms. Examples include: integrating data from multiple levels of analysis; developing data collection, storage, and analytic methods that support integrated multidisciplinary attacks on critical questions; integrating studies of typical and atypical development; integrating human and non-human studies where appropriate; and integrating separate disciplines into team-based science. In fact, a number of workshop participants commented on the fact that the workshop itself provided a welcome venue for promoting integrated efforts and understanding, and indicated that future meetings of this kind would be promising.

We have identified seven scientific opportunities of the next decade relevant to cognition that we describe in the next section. For each scientific opportunity, we present any preliminary questions, necessary development of tools, methods, or approaches, and workforce development issues that were identified by workshop participants.

II. SCIENTIFIC OPPORTUNITIES

Scientific Opportunity 1: With the rapidly expanding capabilities of genomics technologies, along with their ever-decreasing costs, there now exists an unprecedented opportunity to (a) elucidate the genetic features of disorders of cognition that have their origins in childhood and (b) characterize the phenotypic development (i.e., change over time in cognition, associated behaviors; and brain systems) associated with specific neurogenetic alterations.

Although there is current knowledge of the genetic basis of a small proportion of cognitive disorders of development such as Fragile X, Williams and Angelman Syndromes, it is becoming increasingly accepted that the genetic basis of cognitive disorders of development are likely to be due to hundreds if not thousands of individually rare genomic alterations. Next generation sequencing, when applied to large populations of individuals with intellectual disability (ID) has the potential to identify most of the genes in those individuals affected with moderate to severe ID (IQ < 50), and many genes involved in more mild to moderate (IQ 50-70) levels of impairment. Employing large samples there is the potential to identify many of the genetic risk factors that are involved in more etiologically- complex conditions like autism, specific learning disorders (e.g., dyslexia) and specific language impairment. In the next ten years we also have the opportunity to understand the epigenomic and transcriptomic consequences of currently-known neurodevelopmental diseases driven by single gene mutations (e.g., Fragile X Syndrome). Together these discoveries will allow us to chart a map of the functional gene circuitries involved in development of these condition, enhancing our ability for detection and characterization of phenotypic manifestations of these genetic alterations; providing the basis for understanding the neurobiology of these conditions and leading to rational approaches to prevention and intervention.

Known single gene disorders e.g., Fragile X Syndrome, newly identified genomic alterations such as copy number variants as well as those genetic alterations that will be identified in the coming decade provide a unique and important etiologically-defined sample for elucidating the effects of these genetic patterns on the longitudinal development of cognition and underlying brain systems, from the earliest possible ages of examination. Use of new, cutting-edge technologies for characterizing neuroanatomy and brain function, such as diffusion tensor tractography, resting – state functional imaging; high-resolution MRI there is an unprecedented opportunity to examine developmental trajectories of brain structures and networks, along with their relationship to changes in cognition in more etiologically-defined conditions. Longitudinal examination of all those individuals carrying a specific genetic risk marker or set of markers (as opposed to starting with those detected on the basis of already demonstrating a clinical phenotype) will allow examination of the complex interaction of factors leading to development of cognitive disorders as well as those factors that may be protective. Taking advantage of the advances described in #1 above, in ten years it is within our grasp to characterize the development of brain systems and cognitive trajectories for a substantial number of genetic alterations that underlie disorders of cognition in early development. Such studies will clarify diagnostic manifestations of these conditions, provide important insights into mechanisms and sensitive periods underlying development that will suggest targets for prevention and intervention. Such studies provide the potential for insights into the role of the biological (including pre- and perinatal) and psychological environment on gene x brain x behavior interactions underlying the development of disorders of cognition, as well as those contributing to more typical patterns of development. Abnormal patterns identified are also likely to provide a framework for understanding more etiologically complex conditions where the specific genetic underpinnings have yet to be determined.

Together these studies will allow us to ask questions such as: what is the impact of single genes on both the genomic and cognitive landscapes ?; how these landscapes affect other cognitive systems?; what is the impact of genetic profiles (genetic risk markers) on cognitive and behavioral trajectories ?; What is the impact of specific environmental factors and what are the mechanisms through which they exert influence, on the genomic and cognitive landscapes ?; and, what are the necessary and/or sufficient gene x brain x behavior x environment interactions, over time, that lead to changing trajectories of cognitive development. The integration of these perspectives will provide a foundation for developing rational approaches to

prevention and intervention with those disorders of cognition where the pathogenesis is less well understood.

Scientific Opportunity 2: Establish a supramural research program that would accelerate our understanding of relatively neglected areas of research on cognitive developmental disorders and corresponding interventions.

Two related yet distinct manifestations of this opportunity will be described, one involving high-incidence, low severity conditions, and the other involving low-incidence, high severity conditions. Beginning with the high-incidence example, the goal is to understand which cognitive interventions work best for whom, if delivered when, and under what conditions. Most of existing knowledge about the effectiveness of cognitive interventions for high-incidence disabilities such as speech sound disorders, specific language impairment, learning disabilities, and attention deficit disorder is limited to estimates of the average effect shown by a group that receives a single intervention relative to a control group. When such group-level results are examined at the level of the individual child, considerable variability in response to intervention is the norm, as is the existence of a group of nonresponders. We know relatively little about which interventions work best for whom, at which time points in development, and under what conditions. As the diversity of the population of the United States continues to expand, and there are increasing numbers of children whose first language is not English, variability in response to intervention is likely to increase even more. Our knowledge about critical periods of development (i.e., when developmental trajectories are most malleable) is similarly lacking. Complicating the situation is that comorbidity is common for high-incidence disabilities. For example, between 20 and 40 percent of children with reading disability are also diagnosed with attention deficit disorder. Consequently, response to an intervention may be moderated by the presence of a comorbid disability, and it is relatively common for a given child to be receiving multiple interventions simultaneously. We note parenthetically that this issue is not specific to cognitive interventions provided to children, but to practically all interventions that fall under the purview of the National Institutes of Health, extending to medical treatment of cardiovascular disease and cancer for example.

Limitations in budget, in number of researchers, and in number of participants in existing NICHD intramural and extramural research programs precludes making substantial progress in filling this important gap in our scientific knowledge. However, for every participant in a formal study of a cognitive intervention, there are tens of thousands of children who are receiving cognitive interventions in local schools and clinics, and who also are receiving assessments. The recent and ongoing establishment of statewide databases that track progress in essential language-related and academic skills of students longitudinally point the way to an opportunity to complement existing intramural and extramural research programs with a supramural research program that recruits practitioners and their clients into research participation. The advantages and limitations of this kind of research are likely to complement those of the more traditional, smaller-scale studies. For example, compared to the kinds of studies envisioned for the proposed supramural research program, smaller-scale more tightly controlled traditional studies are likely to be better at identifying active ingredients of interventions through carefully controlled manipulations, but poorer at identifying variability in the effectiveness of widely implemented interventions associated with characteristics of the child, the implemented intervention, and the context. We envision a two-way street between the research accomplishments of the proposed supramural and existing intra- and extramural research programs. Knowledge gained from more opportunistic and exploratory supramural research studies should provide promising leads that can be pursued in the smaller-scale, more carefully controlled intra- and extramural research studies. Conversely, interventions that appear

promising in smaller-scale and more controlled settings would be candidates for scale-up studies in the supramural research program.

Turning to what is required to exploit this opportunity, two obvious hurdles that must be overcome are enlisting practitioner/scientists into the enterprise and enlisting participants by obtaining consent from parents and guardians and assent from child participants. Regarding enlisting practitioner/scientists into the enterprise, our interactions with these communities lead us to believe that they would be interested and perhaps even enthusiastic participants provided participating is not overly burdensome and that opportunities are provided for participation in the design of research studies as opposed to only implementation. We believe that professional organizations are well-equipped to facilitate this process, and also to facilitate the workforce training that will be required.. Regarding obtaining the cooperation of parents or guardians and child participants, this may prove to be an initial challenge especially for underrepresented communities. However, research on the hugely disparate rates of participation in organ donation programs across similar countries provides an important clue. When organ donation is the default option, participation rates approach 90 percent. When the default option is not to donate, participation rates hover at 10 percent. Obviously, consent and assent must be obtained for participating in supramural studies of cognitive interventions. However, if the initial contact with parents or guardians conveys the value of including their children's data in an ongoing study, and they are requested to sign a consent form to indicate their consent or their refusal to consent, we anticipate that participation will be the norm rather than exception. Understanding which treatments work best for whom, if delivered when, and under what conditions will advance scientific knowledge and potentially lead to more effective interventions.

The second instantiation of this opportunity is to create large-scale research subject registries of individuals of genetically-defined subtypes of cognitive disorders of early development. The rapidly expanding technologies in the field of informatics, the exponential increase in communication through electronic media by families, researchers and practitioners, along with the potential for rapid advances in identifying etiologically-defined subgroups of individuals with cognitive disorders of development (as described in #1 above), create a unique opportunity for the development of large-scale research subject registries; real-world links between researchers and the community through the development of practice-based research networks and development of publically available databases of common measures focused on disorders of cognitive development.

Subject registries and data bases have transformed research in pediatric cancer. Available resources on common behavior measures and DNA repositories have and will be critical in the advances made in other conditions (e.g., the Autism Genetics Research Exchange (AGRE), Inter-active Autism Network (IAN) and the soon to be available National Database for Autism Research (NDAR)). No such systematic registries or databases exist for disorders of early cognitive development. While behaviorally-defined disorders of cognition are common in the population, as noted above, eventually there are likely to be 100's if not 1000's of genetically-defined subtypes of cognitive disorders of early development, raising the issue of finding research samples of sufficient size for study. In the next ten years the establishment of large-scale, national patient contact registries and common measures databases are feasible goals to accomplish that will transform the field by dramatically increasing research capacity in the areas of behaviorally-defined disorders of early cognitive development such as dyslexia, as well as in those cognitive disorders of early development that are etiologically-defined (e.g., Fragile X Syndrome, 16 p duplication, fetal alcohol syndrome and less common conditions such as urea cycle disorders). Biobanks of DNA and other relevant samples, obtained in systematic ways

and linked to widely-accessible databases will also dramatically expand the scope of research in this area.

Establishment of common behavioral measures will be a critical step in facilitating the development of this scientific opportunity (see below under “Tools”). Related to the development of databases, there is and will be a need for interactive informatics systems to allow rapidly interrogation of the expanding body of available information from the research literature and future databases. Systems should be developed for efficiently extracting information from all of these resources that map on to other interfaces e.g., known molecular networks and brain systems, and facilitate more efficient, practical and flexible access to such information. Such central resources (registries, databases and electronic interfaces) will also promote collaborations as they facilitate mapping of information and data sharing.

Similarly, there is a critical need to develop real-time links between researchers and the clinicians in the community for (a) further development of research registries and databases and (b) to provide real-world access for community effectiveness research.

Tools for facilitating community development of electronic medical records and developing links to researchers and larger-data bases will be of critical importance to bring physicians and other providers into the research community. These links will also facilitate insights that drive policy decisions as well as providing knowledge about health care disparities, the economics of care delivery (e.g., tracking the effects of poly-pharmacy on those with the most severe cognitive disorders and the resultant effects on health care costs) and tracking the effectiveness of real-world prevention and intervention efforts. Such practice-based research networks have been highly successful in disorders such as diabetes and hypertension and could be instituted for the broad range of disorders of early cognitive development. Similarly, links to schools could be developed that would facilitate (a) school-based intervention programs, (b) links between teachers and clinicians (e.g, space in the electronic medical record could be available to teachers through web-based interfaces) and (c) real-world research. Development of guidelines as well as strategic plans (minimal datasets and electronic interfaces) to begin these activities - linking research labs and communities of practitioners, families and teachers can be accomplished over the next five years. Leadership in changing the culture of such integrative research efforts will be necessary, for example in establishing nationally-based IRBs that facilitate cross-institutional interactions. It is highly feasible that initial steps for establishing such patient registries, research data bases and biospecimen repositories, and community-based research networks can be put in place over the next ten years. These steps will ultimately exponentially accelerate research in the area of childhood disorders of cognitive development.

Scientific Opportunity 3: Create a template of normal cognitive developmental trajectories that integrates multiple levels of analysis and sources of data representing genes, brain, and behavior.

There have been remarkable advances in our ability to collect and model data at the levels of genome, brain, behavior, and environment. What is lagging behind is work at the interface of these domains that seeks to integrate multiple levels and sources of data. Although the advances within these domains have, and will continue to produce dramatic advances in current knowledge, efforts to integrate these sources of data are most likely to produce transformative advances. Such advances will be required to resolve paradoxes that become apparent when looking across domains. For an example of one such paradox, identical regions and phenomena in the genome are associated with what appear to be completely distinct phenotypes at the behavioral level. Resolving this paradox is likely to require novel

reformulations of our models of the genome, of behavioral phenotypes, or both. This scientific objective is motivated by the frequently voiced view during the workshop that a better understanding of normative development is prerequisite to better understanding disorder and disease. What makes this an important scientific objective of the next decade is the recent remarkable methodological advances in genomics, imaging, and models of behavioral development that can incorporate multiple levels of data.

Achieving this scientific objective will require answering a number of preliminary of preliminary questions, development of new methods and applying existing methods in new ways, and workforce training. Examples of preliminary questions that must be that must be addressed include: What are the most promising conceptualizations of the interfaces between genes, brain, and behavior across development? What are times of greater and lesser change, and is there evidence of sensitive or critical periods in development? What animal models are likely to be informative for which aspects of cognitive development? Examples of methods related advances that will be required include: Develop better tools for processing, storing, and integrating data generated across different levels of analysis (e.g., multimodal imaging, genetic/neuro-imaging links, computational modeling, capturing dynamic systems); develop statistical, bioinformatics, and data mining tools; and create core informatics centers to support data input, sharing, and multi-level analyses. Regarding workforce training issues, the top priority is to promote and expand team approaches to studying cognitive development. This will require overcoming conventional barriers to interdisciplinary work, establishing team-science based interdisciplinary training programs, and establishing centers of excellence as a means to jump start the field. Implications for public and global health and for the mission of NICHD include defining windows that are opportunistic for educational and therapeutic intervention, providing a baseline template for understanding the natures and sources of atypical development, and improving treatment effectiveness by taking an integrated and multidisciplinary approach to what are integrated and multidisciplinary problems.

Scientific Opportunity 4: Understand the basic molecular and cellular mechanisms in animal models of disorders of cognitive development.

Although developmental disorders of cognition resulting from single genes are likely to be relatively rare and frequently more severe symptomatically than “common” or “complex” forms of childhood neurogenetic disorders of cognition, it is likely that they act on the same or related molecular pathways and cellular processes that are involved in cognitive disorders of development in the larger group of disorders, where specific genetic alterations have not yet been identified. Evidence from existing studies of single gene disorders point to common molecular pathways, converging evidence about common cellular mechanisms underlying these neurogenetic disorders of cognitive development.

As noted in “Scientific Opportunity #1” above, there has been considerable progress in identifying specific genes underlying cognitive disorders of development and there will likely be many more genes will be identified over the next ten years. Discovery of rare variants underlying common disorders of cognition will be to provide a way forward in understanding what are likely to be common underlying molecular pathways and cellular mechanisms. Through the extraordinary advances in molecular genetics over the last decade (e.g., optical genetics) we now have the technological capabilities to identify mechanistic roles for these genes at the molecular and cellular levels in studies of genetically engineered animal models. Taking advantage of these rapidly advancing scientific capabilities, in the next ten years, it is possible to elucidate how dysfunction of the genes linked to cognitive disorders of early development, disrupt major cellular and synaptic functions and common signaling cascades

(e.g., Ras-MAPK signaling). These mechanistic insights will pave the way for the targeted therapeutic approaches for prevention and treatment of these cognitive disorders. New findings from these discoveries in mouse models will then allow us to examine more complex models of gene X gene and gene X environment interactions, providing critical clues to additional molecular, cellular and neural mechanisms operating in humans affected with these conditions.

Regarding questions that must be addressed along the way and methods that need to be developed to achieve this scientific objective, the development of pharmacologic interventions for treatment of cognitive disorders of development will undoubtedly come from pre-clinical animal studies that are dependent on making links between animal and human behavior. But homologies between behavioral phenotypes in animals and humans are rarely compelling. Similarly the degree of shared neural circuitry is often variable and in many cases not known. As a result often drugs that appear promising in preclinical studies do not achieve satisfactory efficacy in studies of humans. Therefore the identification of clinically relevant, phylogenetically conserved behavioral measures that assess comparable domains of function are of critical importance. For which aspects of cognition will it be productive to identify a small number of core domains that are recognizable across species and can be interrogated with standard approaches, stimuli, instruments across studies. Existing examples where this approach is making some headway include models of reward responsivity/circuitry, response to respondent (classical) conditioning, repetitive behavior, behavioral inhibition, cognitive flexibility, locomotor activity, pair-bonding/mating, visual navigation, olfaction, working memory, and territoriality. There are human paradigms that parallel spatial navigation tasks developed for mice, a paradigm for measuring repetitive behaviors and visual exploration in mice that maps on to a similar measure of visual exploration and repetitive behaviors in children with autism using eye tracking. This will take a considerable effort however to validate similar neural mechanisms/circuits that underlie similar behavior constructs. Development of a cross-species toolbox would facilitate this field as well as foster data sharing, integration and aggregation. Regarding implications, if it is possible to develop effective pharmacological interventions for disorders of cognition, it would be difficult to overstate the importance of this for public and global health.

Scientific Opportunity 5: Elucidate the pre- and perinatal risk factors for cognitive disorders of early development.

With the advent of the National Children's Study and other similar, large-scale epidemiologic efforts (e.g., Early Autism Risk Longitudinal Investigation, or EARLI, as part of the NIH ACE Network Studies; and Study to Explore Early Development, or SEED, as part of the CDC CADRE Network) there is an unprecedented opportunity to identify the pre- and perinatal risk factors for common disorders of cognition. The identification of genetic susceptibility factors will help to clarify the role of environmental factors that impinge on given genetic pathways.

Over the next 20 years, the National Children's Study will be following 100,000 children from conception forward through the periods of risk for development of cognitive disorders of childhood, specifically looking at environmental influences. Cognitive disorders will be apparent in the early phases of this study. Such studies also provide an unprecedented opportunity to look at the interaction of genetic alterations and the pre- and perinatal environment, in leading to cognitive disorders of early childhood. Specifically, over the next ten years it is within our grasp to identify currently detectable pre- and perinatal risk factors for cognitive disorders, and begin to get a foothold on understanding the interaction of those risk factors with the multitude of genetic risk markers that will be identified over this same period of time. In the next ten years,

the availability of these data will enable us to answer the question – What are the genetic and pre- and perinatal environmental contributors to variability in atypical cognitive development?

Important preliminary issues that must be addressed include: How do socio-economic factors affect development in at risk populations? How can these mechanisms be modeled and studied in animal models? How do we use global extreme environments to understand the underlying mechanisms that link environment to cognitive development in infants in both the developing and developed world as a way of understanding plasticity? What are the mechanisms that link prenatal stress (physical and emotional) to fetal cognitive development? What are the influences of genetic variants on plasticity and its response to enriched versus impoverished environments? Required tools, methods, and approaches include new assays (including developmental assessments and measures of environment) that permit us to look horizontally and vertically at gene, brain, and behavior and that permit us to look across different human populations; computational methods for analyzing and linking genomic and cognitive landscapes; well phenotyped tissue/brain banks; research tools that are scaled for children with varying abilities and across cultures; a set of tools that crosses species and has good neural specificity and sensitivity and is sensitive to developmental age. The primary workforce development need is an opportunity to facilitate collaborative training among neurobiologists, anthropologists, sociologists, psychometricians, and cognitive scientists and neuroscientists. The implications for successfully exploiting this scientific objective include providing us with tools to identify, prevent and treat populations at risk both in our society and the developing world; possible modifications to the environment (nutritional, educational, experiential) to impact cognitive outcomes; and prevention or reduction of prevalence of prematurity and the effects of prematurity on cognition by understanding its underlying genetic, epigenetic and environmental origins

Scientific Opportunity 6: Develop knowledge of pre-clinical risk and protective markers to guide the establishment of preventative recommendations for optimizing cognitive health.

Following on advances in the field and opportunities described above, the research community in field of cognitive disorders of early development is and will be well poised to take advantage of the wealth of information from studies of genetic risk profiles, pre- and perinatal risk markers, brain and behavioral trajectories and other biomarkers (e.g., nutritional profiles); gene X brain X behavior X environment interactions; as well as links to real-world clinical practice, to begin to provide families and providers with guidelines for optimal development of 'cognitive health', from the prenatal period through early adulthood. This approach would emphasize a model of prevention, similarly to the approach taken in other fields of medicine (e.g., treatment of hyperlipidemia and hypertension – risk markers for later development of cardiovascular disease). Links to community samples and research databases will be critical to facilitate development of risk profiles and to enable large-scale mapping of clinical information (e.g., that available through community-based electronic medical and school records) to functional outcomes relevant to cognitive development (and vice versa – outcomes can be mapped back to risk profiles). Setting up systems to develop such preclinical risk and protective profiles for optimal cognitive health can be accomplished over the next decade. These systems can be constructed whereby information accrues over time and updates our knowledge-base in real time, making information available to practitioners for clinical application, proscribing the cognitive equivalent of proper exercise, diet and environmental exposures as seen in the fields of cardiovascular disease or cancer. There will be a need for systems and knowledge of how to integrate the vast amount of potential information (e.g., personalized genomic data) into the

electronic medical record and clinical practice. The goal is not to gain a complete understanding of such factors within the next decade, but rather to build a framework that will allow for significant strides to be made toward that goal. The vision is to provide the beginnings of a roadmap that clinicians can use that inform them about significant risk factors for suboptimal cognitive outcomes, so that increased monitoring and, if necessary, early intervention and prevention can occur.

Scientific Opportunity 7: Improve the accuracy with which children with learning disabilities are identified, improve the effectiveness of cognitive interventions substantially by developing personalized interventions that are informed by cognitive science, and reduce or eliminate sequelae associated with severe learning disabilities that often are more deleterious than the learning disability itself.

Existing identification procedures for children with learning disabilities are inadequate in at least two ways. First, the accuracy of existing identification procedures has been little studied, but one recent large scale study found that only 20 percent of children who met research-based criteria for reading disability had actually been identified by existing school- or clinic-based identification procedures. Part of the problem appears to be that existing identification procedures require an initial referral by a parent, teacher, or other professional, and that referral appears to be a haphazard process. The second problem is that most children with learning disabilities are not identified until the beginning of second grade, at which point their problems become more intractable than they would have been had been addressed earlier. The solution to substantially improved and early identification is to develop effective universal screening measures that can be given early.

Cognitively-based interventions directed towards improving performance in various intellectual domains are largely uninformed by (a) cognitive science, (b) specific knowledge about the target domain, and specific knowledge about the individual receiving the intervention. Examples of areas of cognitive science that have not been incorporated into cognitively-based interventions include: knowledge about longer-term skill acquisition from studies of the development of expertise; knowledge about what conditions result in near perfect long-term storage of information (i.e., perma-store), what leads to forgetting; and knowledge about what leads to cumulation of effects of training over time. Examples of specific knowledge about the target domain that are not reflected in cognitively-based interventions include the fact that sub skills that vary in difficulty of acquisition routinely receive equivalent amounts of training, and the fact that interventions do not take into account the fact that most domains are characterized by prominent statistical regularities (e.g., if you know X, the probability is high that you also know Y). An example of how specific knowledge about the individual receiving the intervention could be incorporated by cognitively-based interventions is intelligent-tutoring systems that use Bayes nets to keep track of what is currently known by the individual and to select the next learning trial on the basis of that knowledge.

Turning to the issue of reducing or eliminating sequelae, children with severe learning disabilities in reading, approximately 2 to 4 percent of all children, are nonresponsive to any known interventions. In addition to a profound reading problem, children with severe learning disabilities in reading are more likely to develop impairments in other areas such as vocabulary and general knowledge about the world, to not attend college, to drop out of school, and to have poorer career outcomes. These represent sequelae of severe learning disabilities, in that the inability to take in printed information affects vocabulary development, grades, probability of dropping out, career outcomes, and other things like academic self-concept. Remarkably, the outcomes for students with severe visual impairments that prevent them from reading print at all

unassisted are better than those of children with profound reading disabilities. A likely reason for this is that students with severe visual impairments are taught other forms of reading (e.g., Braille, and the use of assistive technology for decoding print) whereas students with profound learning disabilities in reading are not. Assistive technology in the form of computer-based readers offer a potential solution to this problem if this technology is further developed and can be applied more universally.

Turning to questions that need to be addressed to achieve this scientific objective, what is the accuracy of existing identification procedures? Does the accuracy vary by demographic characteristics of the child? What is the most effective, efficient, and cost-effective means of universal screening. Using knowledge about emerging forms of literacy, how early it is possible to screen? If prior to school entry, is there a practical initial form of screening that could be done by a health services provider? Turning to assistive technology, how can computer-based readers be made more practical, portable, and universally applicable. For example, what technological developments would be required to be able to wear a pair of glasses that would contain a miniature camera, the integrated circuitry, and audio output such that print encountered in the environment could be heard in an ear piece? So as not to inhibit the development of unassisted reading from its maximum possible though still insufficient level, what is the optimal combination of assisted reading and intervention directed at improving unassisted reading? How can statistical regularities be identified efficiently across large numbers of domains, and how can these regularities be exploited most effectively? What knowledge is necessary to transition from current interventions that are time-limited to interventions that may extend over years? What form of knowledge model (e.g., Bayes nets) is optimal for improving the effectiveness of cognitive interventions, and how can it be used in training in a wide variety of contexts? For example, existing Bayes net based intelligent tutoring systems are associated with computer-based instruction? How can these systems be adapted to human led intervention, or hybrids of human- and computer-based intervention?

Implications for public and global health and for the mission of NICHD of improving the accuracy of identification and minimizing if not eliminating sequelae of severe learning disabilities would be profound if school and career success improves substantially these children. The availability of more effective cognitive interventions would be important to individuals with learning disabilities but also to other examples of cognitive training including general learning contexts.

III. CONCLUSION

This is a remarkably promising time for addressing scientific opportunities relevant to cognition. We have identified opportunities that exist along the continuum from basic to clinical and translational areas of research. Taking advantage of these opportunities will require expansion of more richly integrative and interdisciplinary research efforts. It also will require a new research program that complements existing intra- and extramural research programs. The goal of this program is to dramatically increase participation in NICHD's research mission by recruiting both scientist/practitioner and participant/clients into the effort.