

Transformative Neurodevelopmental Research in Mental Illness

Report of the National Advisory Mental Health Council's Workgroup

TABLE OF CONTENTS

I. Introduction.....	1
A. Background.....	1
B. Workgroup Charge.....	4
C. Workgroup Progress.....	4
D. Overview of the Report.....	5
II. Framing the Agenda for Transformative Neurodevelopmental Research in Mental Illness.....	6
A. Cross-Cutting Issues in Developing Transformative Neurodevelopmental Research in Mental Illness.....	6
1. NIMH should focus on the ripest basic and translational research opportunities with potential to impact mental illness.....	6
2. NIMH’s portfolio should reflect the importance of longitudinal research in revealing normative and atypical brain development.....	6
3. NIMH should invest in validating tools that basic, translational, and clinical researchers can share.....	7
4. Understanding typical and atypical development requires careful work with a variety of developing organisms, and across species	7
5. NIMH should support studies done directly with developing humans.....	8
6. NIMH should help to expand intervention research with children and adolescents.....	8
7. Investigators need more and easier access to the rapidly evolving information base and to available resources.....	8
B. Research Priorities in Charting the Development of Typical and Atypical Brain and Behavior	9
1. Build the knowledge base of how the brain typically develops, on the molecular, neuroanatomical, and functional levels.....	9
2. Identify and improve the characterization of sensitive, malleable periods of neurodevelopment.....	10
3. Further understand how and why healthy brain development goes awry to result in mental illness	10
4. Understand gene by environment interactions in mental illnesses	11
5. Increase collaborations between developmental epidemiology and developmental neuroscience	12
6. Develop new intervention strategies targeting developmental trajectories.....	13
7. Build resources, develop new methodologies, and promote platforms to facilitate information/resource sharing.....	13

III. Fostering a New Field Through Collaboration.....	16
A. NIMH Should Make a Concerted Effort to Enhance Interdisciplinary Collaboration	16
1. Enhance opportunities to grow new science and scientists using existing Research Project Grant (RPG) mechanisms.....	16
2. Build on established conferences	17
B. Foster a Culture of Sharing Among Grantees.....	17
C. Enhance Collaboration with Patient Advocacy Groups.....	17
D. Support Knowledge Management and Transfer to Ensure Rapid Dissemination of the Newest Techniques, Resources, and Concepts.....	18
E. NIMH and Leadership	19
1. Oversight.....	19
2. Review and funding mechanisms	19
3. Foster collaboration within the NIMH.....	19
4. Create a basic neurodevelopment group within the Intramural Research Program.....	19
IV. Creating an Effective and Well Trained Workforce.....	21
A. Attract Clinician-Scientists.....	21
B. Integrate Research and Training Initiatives.....	22
C. Create Opportunities to Inject Expertise and Knowledge of New Technology into All Levels of the Workforce.....	22
1. Exposure to new knowledge through support for summer institutes or mini-sabbaticals.....	22
2. Fostering expertise through support for institutes or courses that train researchers in new methods.....	23
V. Conclusion	24
VI. Footnotes	24
VII. References.....	25
Appendix A: Council Roster.....	27
Appendix B: Workgroup Roster.....	29
Appendix C: NIMH's Neurodevelopmental Portfolio Fiscal Year 2006.....	30
Appendix D: NIMH Staff to the Workgroup.....	32

I. INTRODUCTION

A. Background

Mental illnesses are real, debilitating, and common. One out of every 17 Americans suffers from a severe mental illness in their lifetime (Kessler et al., 2005b). The burden of mental illness falls on individuals from all walks of life, all parts of the globe, and all age groups (WHO, 2001). Children and adolescents are not exempt; an estimated four million American children and adolescents suffer from a severe mental illness (US DHHS, 1999). With half of all mentally ill adults exhibiting symptoms of mental illness by the age of 14 and three quarters by their mid-twenties, it is increasingly clear that understanding the origins of mental illness requires studies that elucidate the mechanisms of developing brain architecture and chemistry (Kessler, et al., 2005a). This is particularly important given that the onset of symptoms may not indicate the actual beginning of the illness; symptoms may appear long after the causal processes leading to mental illness have begun. Greater understanding of the developmental origins of mental illness offers hope that new diagnostic methods and better treatments will substantially reduce or eliminate mental illnesses¹ such as anxiety, attention deficit hyperactivity disorder (ADHD), autism, bipolar illness, depression, and schizophrenia.

New research in Alzheimer's disease, an illness typically diagnosed in late life, illustrates the distinction between overt symptoms and covert disease processes. Researchers have found a link between a specific variation of the apolipoprotein E gene, known as *ApoE4*, and an increased risk of developing Alzheimer's disease. Results from recent imaging studies have shown that children with the *ApoE4* variant had thinner entorhinal cortices relative to children with other variants of the gene. Because the entorhinal cortices are the first areas of the brain to exhibit the characteristic neuronal tangles associated with Alzheimer's disease, these findings suggest that processes leading to detectable Alzheimer's disease in later life may be silently underway in childhood. With this knowledge, researchers will begin to explore earlier in the lifespan to understand how and when the *ApoE4* variant may contribute to the development of Alzheimer's disease (Shaw, et al., 2007a). Likewise, interventions targeting younger, high-risk populations may have remarkable benefits in reducing the risk for psychopathology over the lifespan. Understanding when and how a factor exerts its influence is essential to defining the mechanism of action of a particular mental illness. In short, researchers must know not only what to look for, but when to look.

The critical role of timing in the onset of mental illnesses is also studied through the use of model systems, as illustrated by recent animal work in the serotonergic neurotransmitter system. Serotonin has been implicated in mood disorders, and drugs targeting this system have often been used in the treatment of anxiety and depression. Researchers found that mice lacking the gene that encodes one subtype of the serotonin receptor, the serotonin1A receptor, will develop anxiety-like behaviors in adulthood. However, if that gene is briefly "turned on" in the early postnatal period, the anxiety-like behaviors will not develop. This is only true for a specific period; turning on the gene later in life will not cause the same protective effects (Gross et al., 2002). Again, researchers must understand the developmental progression of a behavior, trait, or illness to reveal the genetic and environmental causes of onset and prevention.

A series of recent reports by Shaw and colleagues (2006, 2007a, 2007b, 2007c) on ADHD advances both the basic and clinical understanding of the disorder. Parents, teachers, and researchers have long debated the extent to which ADHD reflects a departure from the typical path of brain development or a developmental delay. Shaw and colleagues used magnetic resonance imaging (MRI) scans from youth with and without ADHD to examine cortical thickness in relation to clinical outcomes (2006) and longitudinally as a measure of cortical

maturation (2007b). Children with ADHD and with the poorest clinical outcomes showed global thinning of the cortex, most prominently in prefrontal regions, which are important for attentional control (2006). Shaw et al. (2007b) then examined a novel index of brain maturation, the individual 'inverted-U' trajectories of increasing, followed by decreasing, cortical thickness. They found that the shapes of the developmental trajectories were similar for both children with ADHD and healthy comparison children, yet the children with ADHD attained peak cortical thickness an average of three years later than controls. The frontal and temporal areas showed the greatest maturational delays in youth with ADHD. One of the last areas to mature, the middle prefrontal cortex, lagged by five years in those with the disorder relative to controls. Subsequent work by the same group (2007c) showed that better clinical outcomes and normalization of right parietal cortical thickness were associated with a particular version of the gene encoding the D4 dopamine receptor. Paradoxically, although this particular gene version increased risk for ADHD, it also predicted better clinical outcomes and higher IQ in youth with ADHD than did two other common versions of the same gene.

These research vignettes exemplify the rich progress in understanding the neurodevelopmental origins of mental illness and underscore the challenges and promise that lie ahead. NIMH has invested its resources in both basic and clinical developmental neuroscience research in order to explore the underpinnings of mental illness. Researchers are accruing evidence from fields as diverse as genetics, cell and systems neuroscience, physiology, developmental psychology, and epidemiology to identify the disease processes that presage mental illness. This progress and potential is exciting; nonetheless, connecting the discoveries made through basic science efforts with the clinical reality of mental illnesses has been and remains a challenge (IOM, 2000).

To answer this challenge, NIMH seeks new approaches that can translate basic developmental research to the clinic in order to prevent onset, improve diagnostic accuracy, and create cures. By elucidating the underlying mechanisms of illness, this work will translate theoretical ideas about the development of mental illnesses into testable targets for new preemption and treatment efforts including more personalized care. Such transformational neuroscience depends on adopting a rich and complex approach to research, recognizing that:

- Neurodevelopment is a multifaceted, dynamic process that involves gene-environment interactions resulting in both short- and long-term changes in gene expression, cellular interactions, circuit formation, neural structures and behavior over time. A target that may be present at one moment in time may be absent at another.
- The developmental path is malleable and constantly influenced by numerous interacting external and internal influences (genetic, hormonal, behavioral, environmental, etc.).
 - Any of these intertwined influences may cause neurodevelopmental processes to deviate from a healthy trajectory, with molecular, systems, and whole person-level consequences. Effects of deviation from the healthy developmental trajectory may be seen immediately or later, even much later, in life.
 - Any of these influences may cause an atypical process to normalize with a return to a typical neurodevelopmental trajectory.
 - Any of these influences can initiate compensatory processes that could cause behavior to be normalized, with an alternate, but equivalently functional neurodevelopmental trajectory.
- While it is clear that we must pay much greater attention to the complex processes that shape early life neurodevelopmental trajectories, our understanding of how these processes lead to typical or atypical outcomes is nascent.

Neuroscience that links basic developmental concepts and techniques with clinical questions suggests the transformative power of the new field proposed in this report: **translational**

developmental neuroscience. Translational developmental neuroscience refers to the interdisciplinary community of basic, translational, and clinical developmental scientists who use theories and tools drawn from disciplines including bioinformatics, neurogenetics, cellular and molecular biology, physiology, psychology, neurology, psychiatry, and developmental epidemiology, to work toward a more complete understanding of the origin, maintenance, prevention, and treatment of mental illness. To date, the rapid pace of technological advances and data collection within each single discipline has not been accompanied by equally rapid adoption by the others. New approaches, including cross-disciplinary collaboration, longitudinal focus, and full utilization of technological advances should be adopted to actualize the potential within these disparate yet intertwined fields of study.

To speed new scientific discoveries and their application to the care of mentally ill children, adolescents, and adults, the National Advisory Mental Health Council (NAMHC) called for a workgroup to focus on clinical neurodevelopment at its May 2007 meeting. Council members (see roster in Appendix A) urged inclusion of clinical, translational, and basic researchers, as well as individuals from NIMH's intramural research program (IRP) and from the public. Co-chairs, Pat Levitt, Ph.D. and John March, M.D., M.P.H., were selected to mirror the partnering of basic, translational, and clinical neuroscience (see full workgroup roster in Appendix B).

B. Workgroup Charge

The workgroup was charged with answering the following questions:

- How can NIMH best integrate developmental processes in neuroscience, behavioral science, and psychopathology research to forge a deeper understanding of the pathways leading to mental illnesses? What are the most significant gaps in our knowledge and how can we turn them into new discovery opportunities to find answers? What barriers must be overcome?
- How should NIMH stimulate the discovery of the molecular, genetic, experiential, and environmental underpinnings of mental illnesses in development? What are the areas of greatest opportunity?
- How can NIMH foster translational science leading to the ultimate goals of defining better indicators of risk (e.g., biomarkers), specifying the causal mechanisms responsible for risk and protection, and developing effective preemptive interventions?
- What types of infrastructure support are required to speed scientific discovery efficiently? Research resources? Training to provide a diverse workforce of translational researchers? Are there NIH/NIMH grant and contracting processes that need consideration to facilitate the research or research training efforts?

C. Workgroup Progress

The Chairs and workgroup members identified the materials to review regarding NIMH's portfolio, current initiatives, and past reports. NIMH information, along with related [NIH Roadmap](#) and [Blueprint](#) initiatives, and relevant publications, were made available through a web-based forum that facilitated the rapid dissemination of information and the exchange of ideas among workgroup members. Thomas Insel, M.D., the Director of NIMH, opened the first meeting by encouraging the workgroup members to think broadly about innovative ways to address scientific gaps and opportunities facing the field, as well as the infrastructure and training requirements necessary to support an increased emphasis on pediatric neurodevelopment and its relationship to mental illness. Members were briefed on the Institute's overall portfolio pertaining to neurodevelopment, including both extramural and intramural investments (see Appendix C). In addition, the Directors of the Division of Neuroscience and Basic Behavioral Science (DNBBS),

Division of Developmental Translational Research (DDTR), and the Acting Scientific Director of the NIMH IRP each gave an overview of their division's priorities and investment in research relevant to mental illness from a neurodevelopmental perspective. The workgroup held four web-assisted conference calls and two face-to-face meetings between July 2007 and the January 2008 Council meeting.

D. Overview of the Report

This report seeks to provide recommendations that will enable translational developmental neuroscience to flourish by creating and addressing the complexities of normative and atypical neurodevelopment. **Section II** outlines recommendations to NIMH for fostering translational developmental neuroscience and promoting its role in understanding the neurodevelopmental processes that are associated with the onset, maintenance, and remission of mental illnesses towards the goal of prevention and treatment. Section II also outlines the research agenda for the field, composed of the research topics that are most pressing and feasible for the next five years. **Section III** presents recommendations on how to implement this new field functionally, including ways to increase communication and collaboration within and between the intramural and extramural scientific communities, as well as with patients, advocacy groups, and families. **Section IV** outlines recommendations for active engagement and training of existing and future scientists in order to achieve the goals of translational developmental neuroscience.

The workgroup submits these recommendations in the hopes that speeding the translation of basic neurodevelopmental findings into clinical research, with an eye towards predictive, personalized, preemptive, and participatory care, will help improve the lives of those affected by mental illness.

II. FRAMING THE AGENDA FOR TRANSFORMATIVE NEURODEVELOPMENTAL RESEARCH IN MENTAL ILLNESS

The workgroup envisions that the field of translational developmental neuroscience will transform our understanding of mental illness. This new collaborative science will explore and explain how the healthy brain develops, how neurodevelopmental processes go awry in mental illness, and how to re-position these neurodevelopmental processes on a healthy trajectory. The scope of the required research is vast—from individual genes to cells to neural systems and finally to patients in the contexts in which they live. Bringing the relevant elements from many disciplines and technologies to bear on these questions will require new alliances among skilled researchers. Fostering such alliances may be a challenge due to the significant differences between disciplines in research approaches, which can hinder collaboration and translation. In this section of the report, the workgroup outlines overarching recommendations to overcome these differences and forge new opportunities. This section also highlights research areas, and their concomitant resource needs, that should receive priority consideration at NIMH. It should be noted that the research recommendations outlined here would depend heavily on the successful implementation of the infrastructure and training initiatives outlined in Sections III and IV.

A. Cross-cutting Issues in Developing Transformative Neurodevelopmental Research in Mental Illness

- 1. NIMH should focus on the ripest basic and translational research opportunities with potential to impact mental illness.**

There are many brain-based illnesses; however, NIMH's focus for translational developmental neuroscience in humans, animals, and cell lines should be on the developmental processes implicated in *mental illness*. Although the specific brain regions and processes implicated may change as we learn more about the causes of mental illnesses,

NIMH's emphasis should remain focused on studies that are relevant to *mental illness*. NIMH could partner with other institutes to study the developmental origins of co-morbidity of mental illness with other illness (e.g., obesity, asthma).

2. NIMH's portfolio should reflect the importance of longitudinal research in revealing normative and atypical brain development.

Mental illnesses are disorders of life trajectories beginning before birth and extending into older age. Longitudinal trajectory-based studies of the origins of mental illness during early development are the key to better diagnostic and treatment tools for mentally ill patients. Had researchers taken a cross-sectional approach, they might not have found the important link between genetic variation, clinical outcome, and cortical thickness in ADHD presented in Section I. Variation between individuals can mask detection of subtle, but potentially important developmental shifts within individuals over time. While cross group comparisons at set time points can address mechanisms of development, they detect developmental dynamics that may be critical but variable across individuals. Longitudinal studies involve examining changes in behavior and brain processes over a developmental course within individuals, and can identify change within a developmental process or clinical symptom and link it to genetic determinants and neural correlates. Looking longitudinally, particularly over key transition points, may help elucidate the similarities and differences between periods of development, and determine which periods are more vulnerable to disruption. Longitudinal analyses could also have important implications in therapeutic decisions (e.g., whether a mental illness should be treated similarly in children and adults), and could help clinicians develop individualized treatment, taking into account not only the trajectory of healthy development, but also adapting treatments to a patient's individual circumstances. Finally, longitudinal studies of high-risk individuals that do not develop psychopathology may be valuable in elucidating protective factors, and serve as the basis for developing novel therapeutics.

3. NIMH should invest in validating tools that basic, translational, and clinical researchers can share.

Efforts to unite clinical issues with basic studies have been hampered by a lack of tools shared across these domains. Clinical researchers work with diagnostic categories or assessments that, more often than not, do not lend themselves well to approaches that are used in molecular or systems neuroscience. Current measurement tools are also insufficient to support early life longitudinal studies. Significant knowledge gaps have grown because research designs have historically focused on a single level of analysis, in a single species, at a single developmental stage. The workgroup asks that NIMH encourage researchers to focus on tools that have been validated (e.g., contextual fear conditioning, face processing, object recognition) across multiple levels of analysis and to develop and validate new tools and procedures, including imaging tools, that can be used in multiple species and across all developmental stages. Validated, precise behavioral assays will close the gap between clinical and basic researchers.

4. Understanding typical and atypical development requires careful work with a variety of developing organisms, and across species.

Full understanding of the developmental trajectories of childhood-onset mental illnesses requires studies with developing organisms. Certain neurodevelopmental processes are conserved across species, while other features may be unique to specific model organisms. Researchers can utilize model organisms such as flies, fish, rodents, or non-human primates depending on the question being addressed. Fundamental neuroscience is critical to learning about new developmental processes and signaling systems. Ultimately, however, mental illness is a human problem, so non-human translational studies should be designed to inform understanding of human illness. Ideally, this will involve studies that cross levels

of analysis and experimental platforms; NIMH should encourage the use of similar developmental concepts and designs in both animal and human research. Where possible, studies that directly link experiments in animals and humans should be facilitated.

5. NIMH should support studies done directly with developing humans.

Although the inclusion of children in NIMH-funded research studies is required, the current NIH definition of a "child" includes individuals age 18-21, which means applicants can meet the requirement by including only a small number of post-adolescent individuals. Researchers should reinvigorate their efforts to include a robust sample of children of all ages in high impact, high quality clinical research. Studies that do focus on children should ensure that the ages studied make developmental sense. For example, although in some studies it may make sense to consider children between the ages of 10-13 years to be a homogeneous group, for other designs such grouping could mask important developmental transitions. In addition, particular attention should be paid to periods of rapid developmental transition, such as the transition into and out of puberty, that coincide with changes in the rates and expression patterns of mental illness. Basic researchers should be encouraged to consider the addition of developmental studies in their work as well.

6. NIMH should help to expand intervention research with children and adolescents.

There are unique challenges as well as advantages in advancing interventions aimed specifically at developmentally relevant targets. Interventional research offers a unique opportunity to understand how the brain adapts to both pharmacological and psychosocial input. As translational developmental neuroscience matures, more opportunities for early phase interventional studies in both prevention and treatment will arise. The large numbers of children currently in treatment represent an important resource for, among other things, pharmacogenomic studies of treatment benefits and risks. Although the need for greater attention to early- and late-phase clinical trials in children is clear, Institutional Review Boards (IRBs) are often reluctant to approve such trials. The field needs to address the balance among ethical, legal, practical, and scientific needs in order to facilitate interventional research with children.

7. Investigators need more and easier access to the rapidly evolving information base and to available resources.

New mechanisms to communicate available resources and speed investigator access to biomaterials and datasets are essential for enhancing scientific progress. Rapid availability of these materials will enable new researchers to enter the field quickly and apply their skill sets to the study of the developing brain and its relationship to mental illness. Open access will allow small laboratories to move immediately into testing questions rather than expending resources and time obtaining materials. NIMH should encourage new efforts in this area and continue to support ongoing development of community resources such as NeuroMab², and the Knock-Out Mouse Project³.

B. Research Priorities in Charting the Development of Typical and Atypical Brain and Behavior

In addition to rethinking how research is framed, there are important concrete challenges that will need to be addressed as translational developmental neuroscience emerges. Information on how brain and behavior typically develop across multiple levels of analysis—from molecules to cells to circuits and to behaviors, across cognitive, affective, and social domains—is lacking; such analyses are even rarer for atypical trajectories. Basic science studies of these developmental processes can and should generate research on novel treatment approaches, studied in animals and humans, and on mechanisms of treatment response. The following research foci are high priorities

and essential for reaching the goals of translational developmental neuroscience.

1. **Build the knowledge base of how the brain typically develops, on the molecular, neuroanatomical, and functional levels**

Over the past decade, neuroimaging studies that have compared people with mental illness to healthy individuals have revealed a variety of molecular and functional differences within specific brain areas and circuits. Complementing these findings, basic neuroscience research continues to define, in increasing detail, the circuitry connecting these brain areas and their potential roles in emotional regulation, social function, and cognition. However, the focus to date has been primarily in adult humans and animals. Circuits underlying a complex behavior, however, may differ between adults and infants or even between pre-pubescent and post-pubescent children. Studying transitions in molecular, anatomical, physiological, or cognitive function throughout development will provide a better foundation for understanding how the typical brain develops. Developmental neurobiologists have provided great insights into the development of primary sensory and motor systems, but we do not understand the development of those brain regions and circuits most implicated in mental illnesses nearly as well, and therefore we need greater emphasis in this area. Normative developmental studies will be important to achieving this goal; however, such studies should be conducted with specific, achievable aims.

Specific recommendations:

- **Map the time course of gene expression across relevant brain regions and throughout development.**
- **Document precisely when, during the course of development, cells differentiate, and how they are integrated into circuits related to mental illness.**
- **Develop and adapt methods to examine transcriptional regulatory mechanisms in the brain, including epigenetic factors such as chromatin remodeling.**
- **Establish a systems-level understanding of the neural development associated with cognitive, affective, and social behaviors.**
- **Study human brain development with improved structural and functional imaging approaches, especially in young children.**

2. **Identify and improve the characterization of sensitive, malleable periods of neurodevelopment⁴**

Advancing the field of translational developmental neuroscience will depend on the identification and understanding of the periods of development that exhibit the most dramatic transitions in neuroanatomy, neurophysiology, cognitive abilities, and hormonal states in humans and in model organisms. The integration of information across different areas of study is necessary to identify time points and ages at which brain systems and behaviors are particularly sensitive or have unique functions. It is particularly important to understand sex differences in these developmental transition periods and ultimately how these differences contribute to risk for mental illness. For example, we do not yet understand why adolescent girls are far more likely to develop depression than are adolescent boys (Eberhart, et al., 2006), nor why boys are more likely to develop ADHD (Arnold, 1996) or autism (Zhao, et al., 2007).

Specific recommendations:

- **Identify conserved and novel modulators of key molecular, cellular, and circuit transitions.**
- **Search for new molecular targets and for biomarkers of treatment response via genomic, transcriptional, epigenomic, and metabolomic profiling at transition and other key time points in neurodevelopment.**

3. **Further understand how and why healthy brain development goes awry to result in mental illness**

The challenge in understanding the neurodevelopmental mechanisms that underlie mental illness is to elucidate how genetic, epigenetic, and environmental factors alter the trajectory of development and produce pathophysiology characteristic of specific illnesses. Statistical correlations cannot provide the full picture; longitudinal analyses as well as methodological and conceptual advances are needed to comprehend this complex system. Understanding these mechanisms may allow proactive prevention and early intervention efforts in the formative years rather than treatment in response to symptoms later in life.

It is increasingly clear that, despite significant research efforts, animal models simply cannot encapsulate the full complexity of human mental illnesses. In using animals to model dimensional *components* of a mental illness rather than symptoms or diagnoses (e.g., fear conditioning rather than anxiety, or the emergence of social behavior rather than autism), a profound disconnect between research on animals and humans could be resolved.

Specific recommendations:

- **Rapidly introduce newly identified human genetic variations into model systems (from embryonic stem cells to mice) to determine their effects on neurodevelopment—across time and species, particularly focusing on transition periods.**
- **Develop a core group of behaviorally validated dimensional tasks that can be used across developmental stages and across species to understand the neurobiological underpinnings of neurodevelopment related to mental illnesses.**

4. **Understand gene by environment interactions in mental illnesses**

At present, the specific roles that genes, environment, and their interaction play in typical and atypical development are unclear, especially across the course of mental illness. To date, these interactions have frequently been defined via statistical associations; the time has come to determine actual mechanisms of action. Full elucidation of genetic, non-genetic, and epigenetic contributions to development would profoundly improve our understanding of mental illness. Increasing evidence suggests, for instance, that epigenetics—changes in the regulation of gene activity and expression that are not dependent on primary gene sequence—can have far reaching effects. Effects include potential changes in cell differentiation, maturation, and plasticity that could induce long-lasting or permanent alterations of neural circuits. Better understanding of these mechanisms could contribute to new and improved treatment and prevention strategies, and will support the goal of individualized care, or cure, for each patient.

Specific recommendations:

- **Model the combined impact of newly identified genetic polymorphisms and environmental challenges as moderators of risk for psychopathology.**
- **Develop methodologies to study the impact of experience on epigenetic regulation of transcription during typical and atypical development.**
- **Develop a toolbox of validated behavioral measures and biomarkers in humans that are both change- and time-sensitive, and/or are associated with early adversity.**
- **Use a variety of well-delineated contextual factors (e.g., stressors, hormones) to challenge model systems in order to understand genetic and epigenetic influences on development.**
- **Develop new options for ethologically relevant animal housing and testing conditions in order to elucidate gene-environment interactions.**

5. Increase collaborations between developmental epidemiology and developmental neuroscience

The current generation of epidemiological studies has revealed that mental illness begins early in life and can have diverse manifestations. Genetic epidemiological studies have shown that risk genes are "generalists", predicting, for example, both anxiety and depression (Hettema, et al., 2006). Environmental experience shapes if, when, and how the illnesses actually develop. Understanding developmental trajectories will require the fields of developmental neuroscience and developmental epidemiology to combine their efforts. To date, studies in systems neuroscience have been small and mostly cross-sectional, while larger epidemiological studies have not been informed by knowledge of specialized concepts such as imaging genomics. We can see the benefit of linking the fields through an example from ADHD research. Although it is increasingly clear that one symptom of ADHD, hyperactivity, resolves over time, the cognitive deficits, which are linked to changes in brain structure and function, and have genetic correlates, lead to the greater impairment in the long term.

Specific recommendations:

- **Use methods borrowed from developmental epidemiology (e.g., longitudinal prospective overlapping cohort designs) to study trajectories of related mental illnesses.**
- **Improve clinical phenotyping in research studies, including those conducted with children.**
- **Improve identification of high-risk individuals, including genetic screens, development of peripheral biomarkers for risk, and biologically validated developmentally sensitive measures relevant to mental illness.**

6. Develop new intervention strategies targeting developmental trajectories

Ultimately, the goal of research in this new field is to prevent mental illness from developing and, barring that, to have early and effective intervention strategies that are adaptable for each patient. One way to approach this goal is to target interventions at the developmental trajectory itself, rather than at cross-sectional symptoms. Identification of deviations from typical trajectories in neurochemical development (e.g., serotonergic transmission in autism) may provide a basis for interventions targeted toward specific developmental periods. The great promise is that interventions will guide altered developmental trajectories back to a more typical path, diminishing treatment needs in later life.

The results of the NIMH-funded North American Prodrome Longitudinal Study (NAPLS) highlight the potential of clinical epidemiology in predicting which youth are more or less likely to develop schizophrenia (Addington, et al., 2007). Youth who are going to develop psychosis can be identified before their illness becomes full-blown 35 percent of the time, if they meet widely accepted criteria for risk. The NAPLS study shows that this figure rises to between 65 and 80 percent if youth have certain combinations of risk factors: deteriorating social functioning; family history of psychosis paired with recent decline in ability to function; increase in unusual thoughts; increase in suspicion/paranoia; and, past or current drug abuse. Knowing what these risk factors are—particularly combinations of them—can help scientists predict who is likely to develop the illnesses within two to three years with the same accuracy that other kinds of risk factors can predict major medical diseases, such as diabetes. This type of work will be critical to early identification, and possible prevention or early intervention in at-risk individuals with complex mental illness.

Specific Recommendations:

- **Examine the impact and mechanisms of novel treatments and preventative efforts, including effects on brain maturation.**
- **Develop novel technologies (e.g., virtual reality, robotics, video games) to enable reliable, motivating, personalized, and adaptive assessments and interventions.**
- **Develop biologically validated behavioral interventions that go beyond pharmacological and psychosocial input and can be used in longitudinal studies.**
- **Support the scaling-up and dissemination of empirically validated assessments from cognitive and affective neuroscience research to the clinic to advance diagnostics and intervention.**

7. Build resources, develop new methodologies, and promote platforms to facilitate information/resource sharing.

The technical obstacles to understanding developmental and adaptive changes in cell function due to disease processes are significant. There is a need for high throughput methods that can reveal the functional status of the genome, epigenome, proteome, and metabolome, particularly given that mental illnesses often have polygenic etiologies. While some platforms already exist to analyze cell signaling and altered physiologic status, they are not widely utilized. Technical efforts in cancer and diabetes can be leveraged for use in developmental neuroscience systems. Currently, techniques for gene manipulation and analysis, particularly in mice, are slow, cumbersome, and limited to a small set of known driver lines and tissues. Efforts are currently underway through [NIH's Blueprint](#) initiative as well as at NIMH (e.g., [Development of Recombinase-Expressing \("Driver"\) Mouse Lines for Studying the Nervous System \(U01\)](#), [Tools and Techniques for Elucidating and Manipulating Neural Circuit Development \(R21\)](#)), and should be fully supported. Given the utility of genetic manipulations in understanding gene influences on behavior, novel methods to facilitate this type of research are essential. In conjunction with the NIH Blueprint, partnerships should be explored in which technologies can be adapted rapidly, facilitating the formation of interdisciplinary, technically focused teams.

NIMH investment in an infrastructure for investigators to use and to contribute biomaterials and data would speed the expansion of the field. The organization of this material will require significant bioinformatics expertise up front to establish well-structured libraries/repositories/banks. The greatest impact on addressing current gaps will be in the context of promoting a pre- and postnatal developmental dataset that is accessible and well formatted for additional data analysis by investigators.

Widespread collection of patient samples would enhance genetic studies of mental illnesses. Very large sample sizes, with an informed consent process that permits broad sharing for research purposes, are essential in order to generate valid and usable data. Partnerships with community and patient advocacy groups will be useful in this effort as will the generation of stable networks capable of large, rigorous, and rapid recruitment of appropriate patient populations. Promoting the collection may require investment in mechanisms currently in use at some medical centers, such as linking de-identified biomaterials with detailed clinical data from inpatient and outpatient registries built for retrospective genetics studies. In addition, with new techniques to reprogram human skin cells into pluripotent cells, it is possible to envision universal collection of skin cells from children; with the aim of personalized treatment should a mental (or other) illness arise.

Specific Recommendations:

- **Endorse and expand existing NIH Blueprint and NIMH efforts to develop new *in vivo* transgenic methods, including the use of multiple microRNAs to alter gene expression in specific brain areas and cell types, as well as the generation of inducible *Cre*-driver lines.**

- **Endorse and expand current NIH and NIMH banking and database efforts to include microRNA, splice variants, and a transcriptional atlas of non-human primate and human development with the goal of correlating gene expression with anatomical and molecular information.**
- **Promote widespread collection of patient biospecimens and create an automated deposit system to which NIMH-funded researchers are expected to contribute materials.**
- **Engage bioinformatics researchers to work on new bioinformatics applications, analytic methods, and data management issues.**

III. FOSTERING A NEW FIELD THROUGH COLLABORATION

Scientists cluster where the research opportunities are intriguing, the resources available, and their skill sets apply. New scientific fields emerge and gain momentum when the scientific opportunities require interdisciplinary collaboration and cross-fertilization. Translational developmental neuroscience has emerged from a blend of basic, translational, and clinical neuroscience. A daunting challenge facing this new discipline is the blending of stakeholders from diverse research areas to address the field's most pressing and promising needs. To facilitate this process, NIMH will need to focus on two broad areas of infrastructure development: (1) ensuring that scientists have the opportunity to interact (proximity) and (2) incubating high gain, high risk interdisciplinary science (catalysis). As the workgroup report reflects, some researchers have begun to cross disciplines, learn cutting-edge skills, and establish pioneering collaborations. The core ideas of enhancing proximity and catalyzing new science will define the pathway for fostering collaboration among all stakeholders and within NIMH to support the new field of translational developmental neuroscience.

A. NIMH Should Make a Concerted Effort to Enhance Interdisciplinary Collaboration

1. Enhance opportunities to grow new science and scientists using existing Research Project Grant (RPG) mechanisms.

Multiple Principal Investigators (PI) opportunities and collaborative networks can be funded in a variety of ways:

- **Planning grants:** These would be one- or two-year multidisciplinary R21 networks for the first phase of neurodevelopmental research that includes at least two aspects of the translational spectrum (i.e., basic [animal or human], clinical, and/or practice) or that reaches across levels of analysis (i.e., genes, cells, systems, persons in context).
- **Multidisciplinary Grants:** After the preliminary planning phase, R21s or other team efforts could lead to multiple-PI R01s or multidisciplinary centers on translational aspects of neurodevelopment, and involve PIs from different disciplines submitting applications together. A model would be the [previous ADHD work in 2000-2001](#). These should be reviewed by panels containing experts from multiple disciplines.
- **Administrative supplements:** NIMH is also encouraged to rework the [National Institute of Arthritis and Musculoskeletal and Skin Diseases competitive supplement approach](#). This approach would provide Developmental Supplements in order to promote interdisciplinary collaborations designed to add a clinical component to a basic design or *vice versa*, as well as using additional developmental time points or adding another mental illness.

2. Build on established conferences.

Established conferences (e.g., Society for Neuroscience, Society for Research in Child Development, International Society for Developmental Psychobiology, American College of Neuropsychopharmacology, Society of Biological Psychiatry, American Academy of Child and Adolescent Psychiatry, American Psychological Association) provide a

springboard for fostering collaborations through exposure to innovative ideas. A critical mass of researchers interested in the new discipline of translational developmental neuroscience could meet for a special session at such an established conference, led by a pioneering researcher. This initial effort could grow into a new track within the established conference, eventually developing into a satellite meeting as momentum gathers. Trainees should be encouraged and supported to attend so that they could participate in interdisciplinary strategic planning throughout their training.

B. Foster a Culture of Sharing Among Grantees

Each NIMH grant represents the United States taxpayers' investment in finding causes and cures for mental illnesses; it should be maximized through sharing of data and materials. While there are NIH expectations for the sharing of resources, both in grant applications and via journal publication, there is not a consistent culture of doing so. All too often, researchers waste countless hours in attempts to gain access to material (e.g., gene constructs, plasmids, mouse lines). Moreover, a failure in access can result in expensive duplication of efforts. NIMH should steadfastly continue to endorse sharing among grantees and work with investigators to establish clear benchmarks for sharing.

C. Enhance Collaboration with Patient Advocacy Groups

Many of the central questions in translational developmental neuroscience will require large patient samples. Clinical research efforts could be bolstered by increased communication and new partnerships with relevant advocacy groups. NIMH should continue to solicit, encourage, and facilitate partnerships with community and patient advocacy groups in identifying research questions, designing studies, working with IRBs, recruiting subjects, banking biomaterials, collecting data, and communicating with families about research. Advocacy groups have strong, longstanding relationships with patient groups and families, and this is a substantial advantage in engaging the community, especially underrepresented minority and ethnic groups, in research. One example of a successful effort at bringing families and researchers together is the Interactive Autism Network (IAN)⁶ in which parents can provide information about their child's diagnosis and progress to researchers via the internet. Having information (i.e., genetic, familial, and behavioral) from diverse healthy children and those with mental illnesses will help elucidate differences, and potentially develop appropriately targeted therapies. NIMH should consider establishing large stable networks devoted to screening, assessing, and treating clinical populations of children and adolescents in meaningful numbers. While nascent models for this type of collaboration exist in the form of the Studies to Advance Autism Research and Treatment (STAART) Network and the Child and Adolescent Psychiatry Trials Network (CAPTN) and in a mature form in the NCI-funded Children's Oncology Group (COG), investing in a greatly enhanced infrastructure will be necessary to meet the goals outlined in this report. One promising avenue might be to exploit existing Clinical and Translational Science Awards (CTSA): http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/ to enhance collaborations in the area of translational developmental neuroscience.

D. Support Knowledge Management and Transfer to Ensure Rapid Dissemination of the Newest Techniques, Resources, and Concepts

The workgroup recognized the impossibility of any one person being familiar with the vast array of opportunities available through public and private monies. One good model of the kind of information infrastructure NIMH should explore to fulfill this essential dissemination role is the NIH Blueprint's Neuroscience Information Framework (NIF)⁷, which permits concept-based searches for neuroscience information via the web. NIMH could support the NIF to focus on

developmental neuroscience. Concept-based searches use controlled vocabularies, which can be defined by a community (in this case, researchers) through the use of social collaborative processes like those employed by Wikipedia⁸. Engaging the research community through such processes could facilitate a host of important, but otherwise challenging community-wide activities, such as standardizing protocols, conventions, reference materials, data formats, etc. Another avenue is Scholarpedia⁹, a site with several thousand subscribers, which uses a Wikipedia-like organization to allow for online peer review and widespread dissemination of information in all areas of science. Finally, the development of a forum such as the *Schizophrenia Research Forum*¹⁰, which provides recent updates in the field as well as discussion forums and useful links, would facilitate knowledge transfer to patient-advocacy groups.

E. NIMH and Leadership

From the point of view of both leadership and internal organization, the workgroup believes that the role of NIMH is critical to the success of translational developmental neuroscience. Areas for collaborations among extramural researchers have been previously highlighted, and coordination is needed within NIMH and NIH as follows:

1. Oversight

The NIMH leadership should report regularly to Council regarding progress in implementing the recommendations of the workgroup, and solicit Council members, when relevant, to assist in the process of meeting the goals set forth by the workgroup and embraced by the NIMH Director.

2. Review and funding mechanisms

Recognizing the special barriers that innovative interdisciplinary science may face in review, the workgroup recommends that NIMH ensure the presence of appropriate expertise on review panels within CSR and NIMH review panels. NIMH will also need to find a way to review and support longitudinal studies, which may yield slower or lower rates of publications and, therefore, may not fare well during the review of the competing renewal application. Similarly, it will be important to have a mechanism in place to avoid funding gaps in longitudinal studies that span more than 5 years.

3. Foster collaboration within the NIMH

To an extent, NIMH itself exhibits the same barriers to collaboration faced by the extramural research community. Analogous to the barriers to co-mentoring, there is no formal mechanism within the NIMH for extramural Program staff to share a grant across Divisions—for example, an imaging genomics project shared by DDTR and DNBS. In the context of translational developmental neuroscience, it will be necessary for Divisions to work collaboratively in an effort to create programs that will encourage new research efforts to address the principal gaps described in this report. These collaborations should also extend to the IRP.

4. Create a basic neurodevelopment group within the IRP

NIMH's IRP has played a key role over the decades in stimulating mental health research through both training and research. The current IRP faculty has a proven record in clinical research with strong researchers and a multi-disciplinary focus; however, the addition of a basic neurodevelopment research group would greatly expand the scope of questions that could be addressed. The availability of an entity that is not grant-based would provide a needed and unique resource to developmental neuroscience and has the potential to speed discovery. This new IRP enterprise would require leadership from a preeminent researcher in developmental neuroscience who can encourage a multidisciplinary approach. Ideally, a

basic developmental researcher who is already actively engaged in a dialogue with the clinical community, and who would complement the researchers currently in the IRP would lead the group. Adding this component to the IRP could also enhance this dialog within the research community through the increase in visiting scientists, presentations, and collaborations. It should also facilitate interactions with the extramural community.

IV. CREATING AN EFFECTIVE AND WELL TRAINED WORKFORCE

The new field of translational developmental neuroscience cannot advance without a scientific workforce prepared and trained for the task. Currently, few basic and clinical scientists work across levels of analysis and experimental platforms, and the current pipeline for producing new scientists trained in a cross disciplinary model is weak at best. Mental illnesses are currently thought to be trajectory-based disorders with origins early in life, so it will be necessary to foster collaborations between the large number of researchers who work with adult organisms and the growing number of researchers who work in developmental contexts. NIMH should widen the range of training opportunities available across career levels, to encourage investigators early in their careers—regardless of the degree or discipline—and to support acquisition of new skill sets by established researchers. Training initiatives would provide collaborative research opportunities designed to help forge the new field. Diverse training experiences provide opportunities to attract, train, and retain a diverse workforce. Researchers from different disciplines and levels of seniority can find a match for their particular needs when multiple options are available. The following recommendations are the highest priority items among many needs.

A. Attract Clinician-Scientists

Clinician-scientists are rare in the biomedical sciences: for those focusing on mental illnesses, the period of training is long, and the dual demands of research and clinical care can be challenging to meet. The benefits of initiatives such as the NIH loan repayment program, and mentored career awards, such as the new K99/R00 awards, are promising, but much more is needed. In order to increase interest and to attract and retain researchers into this field, the workgroup asks that NIMH explore how to integrate both research and clinical training into degree programs, bearing in mind the length of training programs. Potential options include adding condensed research training into clinical programs, promotion of dual degree programs such as B.S./M.D., M.D./Ph.D., or M.D./M.S., or novel curricula such as that developed through the [Howard Hughes Medical Institute's \(HHMI\) Med into Grad Initiative](#). Opportunities for mid-career and highly productive senior clinician scientists to either switch fields or expand into a new field will also be critically important for the field to progress.

NIMH leadership are encouraged to engage in conversation with the governing bodies of clinical training in pediatrics, neurology, psychiatry, and psychology in order to develop a 21st-century approach to clinician-scientist training. Although such programs are not directly within the purview of NIMH, advances in translational developmental neuroscience will be greatly hindered without significant near- and long-term improvement in the quantity of clinician-scientists.

B. Integrate Research and Training Initiatives

NIMH-supported Research Centers are attractive venues for developing a contemporary workforce. Although Research Centers do not require or support training, they offer opportunities for individuals to receive experience with cutting-edge research. A synergy can develop between and within Research Centers that extends beyond sharing reagents, participant populations, and behavioral assays. This is already underway; collaborations are being formed between existing research centers. New strategies should be undertaken to take advantage of NIMH's significant

research investments by enhancing both infrastructure and workforce through a far more integrated approach.

C. Create Opportunities to Inject Expertise and Knowledge of New Technology into All Levels of the Workforce

Progress in science requires the incorporation of new knowledge and technologies. In some cases, exposure (that is, knowledge of a particular topic) will suffice; in others, actual expertise in a new technology will be necessary. Growth in translational developmental neuroscience will necessitate substantive opportunities for new and established investigators to gain exposure to multiple scientific perspectives and, in some cases, will require support for developing expertise. To this end, NIMH should provide opportunities for enhanced cross-laboratory and cross-site training, including co-mentoring at all levels of training, as well as T32s (some cross-institutional), mini-sabbaticals, summer institutes and in-depth fellowships. Beyond these general recommendations, the workgroup endorses two specific training initiatives: one focused on exposure to new knowledge, the other on developing expertise in new technology.

1. Exposure to new knowledge through support for summer institutes or mini-sabbaticals

Summer institutes can provide new training and skills, making an attendee conversant or even proficient in a new technology. Currently, training in new techniques to the necessary levels for active research is accomplished through individual effort, in which a laboratory director or other senior laboratory member trains a visiting scientist. While effective, this is a strategy limited in scope, with a few laboratories each capable of training only a small number of external scientists. The process requires a combination of staff time, intellectual property, sufficient funds, and physical space. While visiting researchers often come with money to support their own salary, host laboratories are generally responsible for materials pertinent to the technique, and support is not available for their time as trainers. As this individualized training system is necessary for the dissemination of innovative techniques, NIMH should support and encourage such laboratories to continue their training efforts. One way to encourage these efforts would be to establish mini-sabbaticals where researchers could spend time at a different institution, with the vision of learning and gaining a better understanding of a new component of the emerging field of translational development neuroscience. The NIH Research Education grant (R25) mechanism may be one way NIMH could support this type of training. The training could be structured to allow sufficient time and resources for the visiting and host scientists to establish relationships, ideally leading to the generation of multiple-PI R01 applications, Center Core Grant (P30) or Full-Scale Specialized Center Grant (P50) applications, and other forms of enriched collaborative research.

2. Fostering expertise through support for institutes or courses that train researchers in new methods

Two significant impediments to advances in interdisciplinary science are a lack of support for the widespread adoption of methodologies, and the difficulties inherent in exporting complex, expensive technologies to the broader community.

As widespread adoption of a technique grows, a more efficient and centralized mechanism to support technical training is necessary to meet demand and to ensure consistency in training. The needed standardization could be accomplished through a centralized organization (e.g., summer course, training institute) responsible for core training, which then could produce a manual for widespread adoption by different laboratories. This type of centralized training should increase the number of techniques in each researcher's toolkit,

and provide perspective on the potential application of the techniques. As the goal of spreading particular techniques is achieved, NIMH staff will need to guide the Institute to ensure nimble transitions to the next generation of technical training. Programs that support technical development should be a focus of significant investment and should be linked to training efforts.

V. CONCLUSION

Emerging research into mental illnesses including ADHD, autism, bipolar illness, depression, and schizophrenia shows the promise of linking basic developmental concepts and techniques with clinical questions to transform research into and treatment of mental illness. New discoveries hint at the power of combining research approaches and spanning levels of analysis, but there is more work to do. This report paves the way for scientists from different disciplines to come together over critically important research questions in studies of genes, cells, and systems, in and across basic and clinical settings to reveal how changes along the developmental trajectory of the brain can lead to mental illness. Such essential research will require translation not only from basic findings to the clinic, but also from the clinic to basic research, and will forge a link between researchers focusing on children, adolescents, and adults.

As outlined in the report, studies of this kind will require the establishment of a new field, **translational developmental neuroscience**, and the creation of new resources, enhanced tool kits, and training opportunities. As recent whole genome association studies have shown, very large sample sizes are essential to generate valid and usable data. Instituting a culture of sharing whereby investigators contribute to large open-access banks and data repositories will help broaden research questions, and stimulate cross-disciplinary research. In addition, cross-disciplinary research requires validated tools for use in multiple disciplines, such as behavioral tests adapted for use in adults and children, human or animal. Bringing new and existing scientists to this new field will require innovative training initiatives that can engage investigators at any stage of their careers.

Through the implementation of the proposed recommendations, translational developmental neuroscience has the potential to revolutionize prevention and treatment of mental illness. Identifying the genetic and environmental factors that can contribute to altering the developmental trajectory will help predict which individuals are most at-risk for developing mental illness. New treatment and intervention strategies will emerge based on these research efforts, and may hold the promise that individuals who develop mental illness in the future will receive personalized treatment. By better understanding the typical developmental trajectory, and more precisely determining when and why deviations occur, we may be able to preempt mental illnesses from developing altogether. These goals will require not only the efforts of scientists, but also the help of advocacy groups, parents of children with mental illness, and patients themselves. Though these goals present a daunting challenge, their achievement will transform clinical care and improve the lives of those affected by mental illness.

VI. FOOTNOTES

¹ See the NIMH website: <http://www.nimh.nih.gov/index.shtml> for further information on mental illnesses.

² See <http://www.neuromab.org/> for more information.

³ See http://neuroscienceblueprint.nih.gov/neuroscience_resources/animal_models.htm for more information.

⁴ A **sensitive period** is when the impact of experience is particularly strong over a limited time. A

critical period is the time over which experience can change the state of a developing system, after which fundamental alterations can no longer occur.

⁵ NIH Exploratory/Developmental research grant award. See: <http://grants.nih.gov/grants/funding/r21.htm> for more information

⁶ See <https://www.ianresearch.org/> for more information

⁷ See <http://neurogateway.org/catalog/goto.do?page=.home> for more information

⁸ See <http://wikipedia.org/> for more information

⁹ See <http://www.scholarpedia.org/> for more information

¹⁰ See <http://www.schizophreniaforum.org/> for more information.

¹¹ See A T32 is the NIH designation for an institutional training grant

¹² See: <http://grants.nih.gov/grants/guide/pa-files/par-06-494.html>

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Appendix A: Council Roster

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NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL ADVISORY MENTAL HEALTH COUNCIL**

(Terms end 9/30 of designated year)

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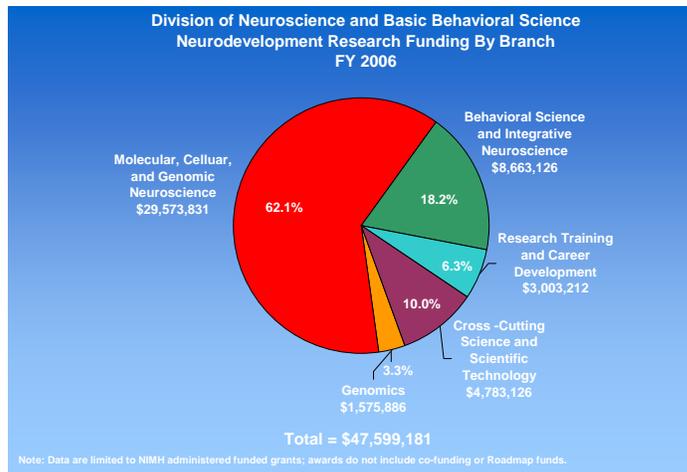
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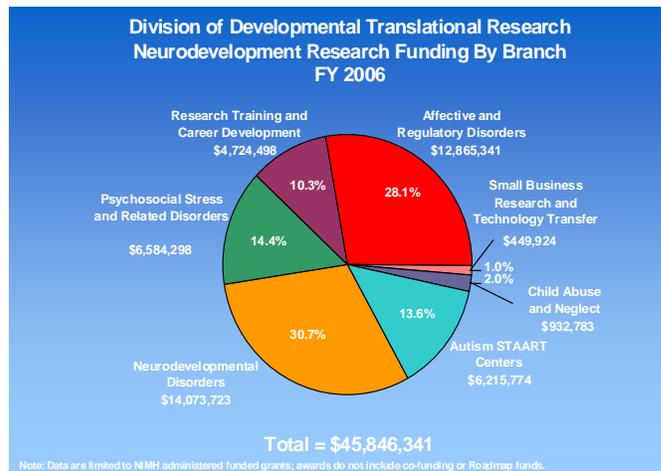
Appendix C: NIMH's Neurodevelopmental Portfolio Fiscal Year 2006

Division of Neuroscience and Basic Behavioral Science (DNBBS)



Linda Brady, Ph.D., Division Director of DNBBS, identified three primary areas of opportunity within the DNBBS research portfolio related to neurodevelopment: interactions between genes, environment and development; key transitions in typical development; and the use of model systems and organisms. Within the area of gene by environment by development interactions, Dr. Brady emphasized the Division's strengths in human genetics, including the genetic cell line repository, and mouse genetics and genomics research. Dr. Brady emphasized the need for a better understanding of neurodevelopmental and behavioral effects of genetic risk alleles, of molecular and environmental effects on mechanisms of neurodevelopment, and for a clarification of the roles of genomic, hormonal, stress, and epigenetic modifications on development. The Division's current portfolio seems adequately invested in research related to adult circuit function and genetically modified mice, with an increased focus on molecular and cellular neurodevelopment, all of which will inform future work examining key transitions in typical development. Dr. Brady suggested that development of prefrontal-cortical-to-limbic circuits, post-natal development, and the role of glia are possible areas for new emphasis, as well as the development of new behavioral paradigms, clarification of transitions in human brain development, and human social development. In terms of model systems and organisms, Dr. Brady noted strengths of the NIMH portfolio, as the Division currently supports research with genetically modified mice as well as the NIH Blueprint for Neuroscience Research and the Knockout Mouse Project (KOMP) initiatives. Dr. Brady suggested mechanistic studies of developmentally relevant molecules, genes, and risk factors via simpler systems, bridging the gap between physiology and behavior, and the development of models to elucidate typical development and transitions as potential opportunities for growth within the portfolio.

Division of Developmental Translational Research (DDTR)



Molly Oliveri, Ph.D., Division Director of DDTR, underlined the strengths of the current portfolio, including a growing portfolio of human developmental studies that includes neuroimaging, electrophysiology, and neuroendocrine function. Other strengths include the growing number of cross-disciplinary efforts involving basic scientists who also have a strong working knowledge of clinical disorders, risk processes, and human development; a focus on development from the prenatal period through adolescence; and a unique resource—the NIH MRI study of typical brain development. Dr. Oliveri detailed the goals of the MRI study as understanding typical development, the creation of age-specific neural templates for studying disorders in children, establishing a link between brain maturation and neurobehavioral and cognitive development, and the development of new image processing tools. Dr. Oliveri presented several areas of opportunity in the portfolio. These areas include a focus on developmental factors, such as timing and plasticity, in studies of specific neurobehavioral mechanisms; the need for increased synergy between animal and human studies and between mechanistic and intervention research; the need for innovative training opportunities; and, the need for improved and more ethical techniques to study human brain development.

Division of Intramural Research Programs (IRP)

Richard Nakamura, Ph.D., Acting Scientific Director of the IRP and Deputy Director of NIMH, reported the success of the current team of intramural researchers, especially in the following areas: cognitive neuroscience; genome-wide association studies; neuroimaging; environment and medication interactions; and development of animal models of specific disorders, such as depression and bipolar disorder; and pediatric mental illness. Dr. Nakamura noted the opportunities that exist within the IRP, especially in areas of infrastructure development and the development of new cognitive tasks to help understand key transitions in development. Thomas Insel, M.D., the Director of NIMH, added that the IRP presents a unique opportunity to conduct research that may not be possible in a more traditional academic system. Drs. Nakamura and Insel suggested that the IRP could be seen as a national resource, and the committee may want to consider ways to maximize its impact.

Appendix D: NIMH Staff to the Workgroup

NATIONAL ADVISORY MENTAL HEALTH COUNCIL (NAMHC) NIMH Staff Contributing to the Workgroup on Neurodevelopment

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