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Eunice Kennedy Shriver National Institute of Child Health and Human Development

Scientific Vision Workshop on Plasticity

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Workshop White Paper

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I. Introduction

Included in the NICHD mission is to ensure that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation. As part of this mission, the Institute supports research on the body's natural ability to repair itself and adapt to injury or disease. This healing property of the body is commonly referred to as "plasticity." It includes adaptive or maladaptive changes in structure and function of cells, tissues, and organs in response to endogenous and exogenous environmental changes, including use and disuse, chemical environment and gene expression, disease and trauma and social and cultural environments. The term "plasticity" is most often used in reference to the central nervous system (i.e., neuroplasticity). Anatomical plasticity encompasses processes invoked during repair of the injured nervous system, including regeneration of injured axons, compensatory sprouting of spared axons, and proliferation of stem cells. Physiological plasticity encompasses processes such as long-term potentiation and other changes in synaptic efficacy invoked during memory and learning. However, almost all tissues are subject to plastic changes during development and in response to environmental change.

II. Workshop

The workshop convened approximately 50 scientists from a variety of disciplines. Approximately half were basic scientists and half were clinical scientists. Approximately a third of participants were young investigators. Three sets of questions (A, B, C) were presented with 2 working groups assigned to address each set. A concerted effort was made to ensure that each group had the appropriate mix of basic and clinical scientists and established and young investigators in order to add balance and perspective. The participants were asked to address the following:

Set A: Basic Science

1. There are a large number of plastic phenomena, each of which is postulated to be explained by different specific mechanisms. Are there one or a few fundamental principles that can unify all of these phenomena at the level of molecular, cellular and systems mechanisms that are valid across the domains of motor, sensory and cognitive systems? Can these principles explain our present understanding of plasticity? Can these principles predict new observations and thereby provide opportunities for the refinement and validation of the principles through new experimentations? What research tools need to be developed or applied in order to further refine and validate these principles? Do these principles provide clues for the future development of diagnostic approaches and clinical interventions?

Set B: Clinical Science

2. What therapeutic approaches and parameters (e.g., intensity, frequency, duration) can we use to affect plasticity in order to restore function within the following domains: Motor, sensory, cognition and pain?
3. What research, diagnostic or therapeutic tools need to be developed or applied to plasticity in order to make substantial clinical progress with respect to impairment, activities limitation, societal participation and quality of life?

Set C: Translation

4. What are the approaches that will facilitate and expedite the translation of plasticity research into clinical practice?
5. What innovative training and other workforce development activities should be pursued in order to promote research in plasticity and application of new knowledge to clinical needs?
6. How can we disseminate new therapies: Health services and implementation research?

III. Scientific Opportunities

As a result of their deliberations, workshop panelists identified several scientific opportunities that could be addressed profitably within the next 10 years. Scientific opportunities refer to emerging scientific developments or advances with the greatest potential to answer the most important research questions or public health issues related to plasticity. The most promising scientific opportunities are discussed below.

Scientific Opportunity 1: Determining whether plasticity represents a single fundamental property of living systems.

Why it matters. How plasticity is used therapeutically could be greatly influenced by whether different modes of plasticity converge on common mechanisms or are totally separate in their signaling and control pathways. Plasticity is a developmentally determined property that allows cells and systems to adopt new phenotypes in response to perturbation in the internal and external environment. This property might be modifiable by switching, or controller, elements that confer stability on the system. At first glance, many forms of plasticity would seem to have little in common. Some forms of physiological plasticity are Hebbian, i.e., they require coordinated activation of synaptic inputs onto close dendritic locations, generally leading to NMDA receptor-mediated increases in intracellular calcium. These modes of plasticity involve highly localized changes in membrane excitability, and do not require changes in gene transcription. Other forms of plasticity clearly do require transcriptional changes in the nucleus, *e.g.*, the plasticity in fate specification of embryonic stem cells, depending on environmental factors. Some forms of plasticity involved in normal development have very different critical ages, e.g., the acquisition of binocular vision and the ability to acquire a second language without an accent. And while some forms of plasticity are homeostatic, i.e., they tend to restore a system to a predetermined set point (e.g., eating habits are adjusted according to weight, serum sodium concentration or glucose levels), other types of plasticity are not (e.g., the allodynia that develops after partial nerve injury). It seems likely, therefore, that the cell may exist in a malleable or a stable state with regard to multiple forms of plasticity, each under the influence of a different stabilizing controller. We do not yet know what these stabilizing factors or switches are, how many there are, or whether they are truly independent of each other.

Implications for the pathogenesis of complex brain diseases. Until now, plasticity has been thought of primarily in regard to responses of the body to dramatic acute pathological processes, such as brain or spinal cord injury. But it is possible that dysregulation of plasticity plays a role in more subtle, yet profoundly disabling conditions. Some diseases and intractable injuries may turn out to be due to dysregulation of these stabilizing factors. Potential regulators of these processes include: Changes in gene product or protein trafficking, epigenetic factors, and environmental variations. Depending on location in the body, cell type and developmental state, each of these factors, alone or in combination, could lead to a different disorder, *e.g.*, neurodevelopmental disorders such as learning disabilities, autism, ADHD, schizophrenia, or Asperger syndrome. By understanding how different forms of plasticity are controlled, it may be possible to better understand these complex disorders and to devise more effective treatments for them.

Implications for therapeutic interventions. This scientific opportunity proposes to test the hypothesis that plasticity reflects the removal of these stabilizing factors that shift the cell from a relatively determined to a flexible state. The testing of this hypothesis could be critical in harnessing the body's plastic properties to achieve therapeutic results. It might be that one or a few treatments could be found useful to enhance many types of plasticity. On the other hand, if there were both positive and harmful consequences to enhancing plasticity, and if all forms of plasticity depended on a common signaling pathway, then ways would have to be found to neutralize the harmful plastic responses while promoting the positive ones. For example, there is evidence that the chronic pain often seen after injuries to the spinal cord may represent a type of physiological plasticity in synaptic transmission. If all forms of plasticity shared a common signaling mechanism, then treatments that promoted regeneration of axons in the injured spinal cord might result in increased pain transmission in patients suffering from that pathological pain syndrome.

New tools and approaches needed over the next 10 years. In order to discover these switches/controllers, and to apply this knowledge in the diagnosis and treatment of disorders, including those that are due to plasticity dysregulation, we need to learn more precisely how brain injury or damage to other tissues triggers plasticity and how to promote its beneficial effects while avoiding its adverse consequences. This will require development of new tools and approaches. We must develop biomarkers that identify the evolution of altered states of plasticity (also see **Scientific Opportunity 2**). There is an enormous number of intersecting signaling pathways that potentially might lead from any perturbation to any plastic change. To make sense of these we must determine whether some signaling pathways are selectively activated during plastic changes. This will be helped immeasurably if we can develop the ability to track signaling pathways in real time. To this end, it will be invaluable to develop non-invasive imaging methods (optogenetic biomarkers or unique intracellular reporter molecules) that are sensitive to altered states of plasticity, and non-invasive microstimulation methods (tomographic or optogenetic methods) that can more precisely determine the pathways involved in plastic changes underlying functional recovery from injury or disease. Similarly, we should develop methods to track changes in synaptic connectivity and concomitant alterations in gene expression and epigenetics during the course of training, injury, and other alterations in pathway use. Understanding the changes in intracellular signaling, gene expression and epigenetic modification that underlie plastic changes will allow us to harness these processes in order to repair injured tissues and to manipulate plasticity in the interest of enhancing functional recovery. Finally, many of the new biomarker, microstimulation and behavioral methods will involve manipulations of massive amounts of data. This will require development of improved bioinformatics methods to analyze the data in a non-invasive and temporally precise manner (also see **Scientific Opportunity 2**).

Conclusion. Manipulation of plasticity in the nervous system could be used to restore or enhance function and quality of life for: Persons with traumatic injuries to the brain, spinal cord, and peripheral nerves; persons with damage to the nervous system due to stroke or other neurological catastrophes; and persons with chronic pain. Manipulation of plasticity in other tissues can be used to restore function through the use of stem cell technology, physical therapies, and other interventions. Thus there is great potential for NICHD to achieve many of its most important goals if we better understood and could better control the mechanisms that underlie plasticity of cells and tissues.

Scientific Opportunity 2: Quantify the evolution of states of plasticity, define critical therapeutic windows for interventions, characterize recovery trajectories and improve prognostication.

Why it matters. As noted in **Scientific Opportunity 1**, the ability to determine altered states of structural or functional malleability will provide clues to switching or controlling elements that modulate plasticity. Injury or disease may create sensitive times or environments that will better enable therapeutic approaches to plasticity. Understanding the regulation of the temporal window for plasticity may lead to strategies that extend the window for therapeutic interventions. Identifying variables that correlate with or predict responses to specific therapeutic interventions will facilitate prognostication, identify methods for determining patient risk, refine eligibility criteria for clinical trials, and improve therapeutic yields in clinical trials and clinical practice. Understanding factors that differentiate non-responders and responders will help define “treatment success” and thereby, objectify study outcomes, provide clues toward the development of novel interventions for the “non-responders” and improve prognostication.

New tools and approaches needed over the next 10 years. The key to achieving this scientific opportunity is the identification of appropriate biomarkers. Plasticity is affected by a variety of factors including age, etiology, location and degree of injury. However, biomarkers can be defined at multiple levels of analysis and these levels are not necessarily independent of one another. Thus there is a need for integrated molecular, cellular and systems level analysis tools. These tools need to be standardized with demonstration of appropriate psychometrics. Once developed, these biomarkers will improve the quantification of altered states of plasticity, define critical therapeutic windows for intervention, characterize recovery trajectories and improve prognostication.

Non- or minimally invasive technology to visualize novel biomarkers of plasticity is needed. In addition to specific biomarkers noted for **Scientific Opportunity 1**, tests should be developed to measure vision, hearing, tactile, smell, taste, and hypersensitivities of sensory functions, particularly in young children. Standard measures like EEG, and new imaging modalities like Near Infrared Spectroscopy (NIRS) are very promising as indices of the intactness of these sensory functions in infants and toddlers. Novel means of temporally regulated, reversible manipulation of circuit-specific activity affecting plasticity (positively or negatively) (e.g. optical methods, improved – more selective TMS), should be developed, both as effectors and outcome measures. Approaches to pain will require better tools for localization, anatomic etiology and objective scoring of severity and intensity; biomarkers are required to objectify the pain experience. Identification of biomarkers correlating with cognitive dysfunction would improve diagnosis and response to therapeutic interventions. However, optimization of tools for functional imaging, neurochemistry and neurophysiology with improved links to computational modeling is needed for the study of cognition.

The integration and analysis of biomarker data will require enhanced, sophisticated databases capable of handling massive amounts of data. For example, in pursuit of **Scientific Opportunity 1**, bioinformatics methods that will allow us to more holistically synthesize the system states being analyzed by new biomarker-, imaging-, and microstimulation-based techniques in a non-invasive and temporally precise manner are needed. The gaps in our understanding of the link between plasticity at the molecular, cellular, and systems levels also present an enormous bioinformatics challenge (the canyon problem). Multimodal analysis and links to neurocomputational models integrating results from imaging, behavioral, physiological, functional and health related quality of life assessments will require tools from rapidly developing computational approaches such as dynamic systems modeling; these techniques can assess lawful relations between change and stability across multiple levels of analysis (from molecular to systems) and will be useful in charting response to treatment trajectories.

Conclusion. The application of basic science understanding of mechanisms of plasticity to achieve clinically-relevant goals will rest to a very great extent on our ability to manipulate massive amounts of data. The key to realizing **Opportunity #2** will be the development of high throughput biomarkers and the more powerful bioinformatics tools needed to analyze them.

Scientific Opportunity 3: Develop valid preclinical models.

Improving the translational nature of basic research. There is significant need for preclinical models and experiments that more accurately reflect the primary and comorbid disease states in humans, and can verify that the repair and plasticity mechanisms under study most closely reflect human conditions. Consistent with **Scientific Opportunity 2**, biomarkers that are relevant across species, such as TMS, fMRI and DTIMRI should be developed to increase generalizability. Efficacy thresholds for moving basic research findings to first-in-human studies should be clarified. In addition to mechanisms, preclinical models and experiments should track clinically important outcomes such as pain, activities limitation, social integration and quality of life, which have broad personal and societal implications. This will help ensure that mechanisms and therapeutic outcomes observed in preclinical models and experiments will be reproduced in clinical trials and ultimately translate into actual clinical practice.

Collaboration between basic and clinical scientists. A key factor in successfully pursuing this opportunity is the formation of collaborative working relationships between basic and clinical scientists. A concerted effort should be undertaken to eliminate discipline-specific "silos" and create a culture and a common language to foster collaboration among basic and clinical scientists, especially with respect to the design and implementation of preclinical experiments. Funding mechanisms that require a basic and a clinical scientist as co-PIs may be strategic in this regard. Mechanisms for training clinical scientists in the basic sciences already exist (e.g. K08). The development of similar mechanisms for training basic scientists in clinical research should be considered. Interdisciplinary centers in plasticity that promote interactions between basic and clinical scientists, other disciplines and other centers may further reduce the "silo" effect.

Conclusion. There is no way to predict absolutely which basic science discoveries will have clinical importance in the long run. Nevertheless, it is possible to target basic science more accurately toward clinically significant goals, and many otherwise excellent basic science studies could have been predicted to be inapplicable to human conditions, had the translational aspects been more carefully evaluated. Key to improving the translation from bed to bedside will be to encourage greater communication and collaboration between basic and clinical scientists.

Scientific Opportunity 4: Optimize plasticity-based clinical interventions and demonstrate their effectiveness in clinical trials.

Improved clinical trial design would enhance plasticity-based therapies. Efficacy trials emphasize internal validity and tend to focus on mechanisms, impairment-based outcomes and comparisons with placebo. Efficacy trials already have validated numerous plasticity interventions, including constraint induced movement therapy, robotic therapy, mental practice, bilateral movement therapy and electrical stimulation. However, prior to acceptance by the clinical community, these interventions need to be optimized with the elucidation of the appropriate content, dose and duration of treatment, and the identification of optimal patient characteristics, including clinical features, demographics, personality, social and environmental factors and other biomarkers. Dose response studies are critical and should be based on effects on plasticity, as well as toxicity and tolerability. While clinical studies typically follow the elucidation of mechanisms, they may also inform the design and implementation of additional mechanistic studies to further optimize the intervention. Thus collaborations between basic and translational scientists (see also **Scientific Opportunity 3**) can have bi-directional benefits and should proceed simultaneously. Once optimized, the intervention should be evaluated in an effectiveness trial that compares the intervention to the standard of care to maximize external validity. These effectiveness trials should focus on clinically relevant outcomes, including activities limitations, society participation and quality of life, with careful consideration of cultural, environmental and social factors (see **Scientific Opportunity 6**). Given compliance issues, resource limitations and the potential role of social and environmental factors in clinical outcomes, emphasis should also be placed on the development of community and home-based monitoring and therapies.

Need for better mechanisms to support clinical optimization research. Proposals that seek to optimize an intervention can experience significant challenges in the NIH peer-review process. Establishment of alternative mechanisms to facilitate support for these vital, but more incremental optimization and baseline studies should be implemented. In order to analyze outcomes of highly complex disorders, clinical trials will have to be highly stratified, which will require access to a large population of patients. The widespread adoption of electronic medical records will be vital in this effort. Due to the nature of clinically relevant outcome measures, effectiveness trials will also require large sample sizes. The development of plasticity-specific national research networks or the utilization of established CTSAs and other existing networks may facilitate the recruitment of numbers of research participants that are large enough to encompass representative ethnic, race, culture, gender and age distributions. Such networks will also facilitate standardization of methods within and across centers and provide access to statistical, methodological and data management resources.

Conclusion. As the quality and complexity of clinical research grows, it becomes clear that the validity of the research is dependent on research design. Methods to optimize clinical plasticity-based studies may be as important as those establishing proof of principle. Therefore, it is vitally important that mechanisms be developed to support both the optimization tools and the studies themselves.

Scientific Opportunity 5: Evaluate the effects of combination therapies on plasticity.

A single intervention may not show clinically important health impact. Thus, combination therapies should be explored. Combination therapies might include drugs, specific physical and occupational therapy interventions, assistive devices, robotics, electrical stimulation, virtual reality, games and cognitive behavior therapy. However, different therapies may affect different aspects of plasticity and may be synergistic or antagonistic in combination. The relationship between any individual behavioral intervention and the associated plasticity mechanisms is not likely to be linear. This relationship will be even more complex in the context of combination therapies. The specific plasticity mechanism associated with each individual intervention should be identified. The successful completion of **Scientific Opportunity 1** will be essential in this regard. A theoretical framework should be developed that accurately predicts the interactive effects of multiple interventions. This framework can then be tested by informing the design of combination therapy interventions that match the patients' biomarkers with respect to their disease or injury mechanism and prognostic factors.

Scientific Opportunity 6: Elucidate the mechanistic relationship between plasticity, activities limitations, societal participation and quality of life.

Mechanistic studies typically focus on the biology of plasticity. However, the ultimate goal is to have an impact on clinical effectiveness, and clinical effectiveness is measured at the level of activities limitation, societal participation and quality of life. Thus if we are to affect the overall health and wellbeing of Americans, mechanisms that explain the relationship between the biology of injury, disease, recovery, repair and response to interventions, and the clinically relevant outcomes of activities limitation, societal participation and quality of life must be understood. The important and substantial role of the environment and social factors on disease and injury manifestation, recovery trajectories and response to intervention is becoming increasingly apparent and needs to be further evaluated and understood. As noted for **Scientific Opportunity 3**, collaborative relationships between basic, clinical and social scientists may facilitate the elucidation of these complex relationships. Once these relationships are understood, treatment paradigms may be optimized accordingly to maximize health impact.

IV. Process Opportunities

Process opportunities refer to infrastructure, policy and culture related processes that may be beyond the scope or influence of the NICHD or even the NIH in general, but are essential if the innovations incubated, developed and tested in the basic and clinical sciences are to ever translate into actual clinical practice. The workshop participants emphasized that if the goal is translation of scientific discoveries into clinical practice, these opportunities, although not necessarily scientific by themselves, need to be pursued in earnest.

Process Opportunity 1: Develop strategies that facilitate the adoption of new therapies into clinical practice.

As in other fields, investigators in plasticity research must secure intellectual property and develop strategic relationships with industry to foster technology transfer. Engaging the commercial/industry community in high-risk, high-gain research mechanisms via competitive incentives may further enhance relevance and expedite clinical translation of research ideas. Participatory Action Research where stakeholders, including patients and “gate-keeper” clinicians, are involved in research development, recruitment, implementation and dissemination will increase the likelihood of a “buy-in” of new therapeutics by the community. As new therapeutic approaches become available, clinicians should be trained as instructors with the incorporation of emerging techniques into clinical training programs (e.g., residency and fellowships). Other training opportunities include the continuing education mechanisms of professional and advocacy organizations and web-based and other emerging technology learning approaches. Finally, medical professionals should engage in intelligible, science-based, culturally relevant conversations with the patient community regarding advances in plasticity research and treatment.

Process Opportunity 2: Harmonize federal regulations and policies related to the conduct of research, approval of drugs and devices and reimbursement for clinical services.

Representatives of federal research, regulatory and healthcare funding agencies should enter into a dialogue to review and evaluate the impact of their respective regulations and policies on the process of scientific discovery and translation to clinical practice. Representatives should identify and retain those regulations, policies and requirements that are consistent with one another or provide complementary purview. However, redundant or conflicting regulations, policies and requirements should be harmonized or eliminated. The translation of drugs and devices into clinical practice requires regulatory approval that can often be cumbersome and costly; streamlining of this process without jeopardizing patient safety will facilitate the translation process. Translation also requires the means for paying for the interventions. Third party commercial payers often follow CMS policies and decisions regarding coverage for services. Reasonable reimbursement practices for effective innovative therapies should be defined.

V. Overall Conclusions

As part of the NICHD Vision process, the NICHD Plasticity Workshop brought together 50 scientists from various disciplines to identify the most promising scientific opportunities in plasticity research for the next decade. The participants identified 6 key scientific opportunities in the areas of basic science, clinical science and translation. Together, these opportunities will lead to advances in our understanding of the many forms of plasticity expressed in our bodies, and this in turn will lead to an improved ability to harness the body's plastic properties in order to enhance recovery from injury and disease. In recognition of the NICHD mission to meet pressing health needs, the opportunities also reflect the importance of maintaining clinical relevance in our scientific endeavors, and the need to elucidate the relationship between the biology of plasticity and the health related outcomes that reflect clinical effectiveness. The participants also identified process opportunities to help ensure that innovations incubated, developed and tested in the basic and clinical sciences translate into actual clinical practice. Together, the successful pursuit of these scientific and process opportunities will have a profound impact on the health, productivity, independence, and well-being of all people.

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