1

Introduction

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Brain and nervous system disorders are the leading cause of disability worldwide and the primary overall cause of disease burden[1] in established market economies (Murray et al. 2012; Vos et al. 2012). Some brain disorders are important causes of death, most notably stroke and suicide (for which the far most potent risk factor is a mental illness). However, the overwhelming impact of brain disorders on societies and their economies results from their highly disabling effects (Bloom et al. 2011). After all, the brain is the organ of thought, emotion, and behavioral control; thus brain disorders not only cause suffering and stress in individuals and families, they also interfere with the ability of young people to learn in school, for adults to work, and, when severe, with the capacity for self-care. In addition, depression and other brain disorders significantly worsen the course of other chronic diseases, including heart disease and diabetes mellitus (Moussavi et al. 2007).

Developmental neuropsychiatric disorders, such as autism and schizophrenia, and mood and anxiety disorders have very high aggregate prevalence, begin early in life, and are either chronic or exhibit a relapsing and remitting course. With a growing proportion of the world's population living past the age of sixty years, the prevalence of highly disabling neurodegenerative disorders, such as Parkinson disease, Alzheimer disease, and other forms of dementia are projected to increase dramatically in upcoming decades and to entail staggering costs—not only direct medical costs, but also costs resulting from removal of caregivers from the workforce (Hebert et al. 2013).

Despite the severely negative impact of brain and nervous system disorders facing individuals, families, and societies, our current arsenal of effective therapies is extremely limited and remarkably dated. The molecular targets of the major classes of drugs to treat psychosis, depression, and anxiety have not changed from the prototypical drugs discovered serendipitously in the 1950s. Lithium, the therapeutic properties of which were surmised in 1949, is still a mainstay of treatment for bipolar disorder, as is L-DOPA, which was first used

[1] Disease burden is widely measured by disability adjusted life years (DALYs), the present value of future years of healthy life lost to premature mortality (YLL), and years lived with disability (YLD).

in 1961 for Parkinson disease. For many common brain disorders, including depression and schizophrenia, the efficacy of drug therapies plateaued more than a half century ago. Moreover, there are still no effective drug therapies for the core symptoms of autism, the cognitive symptoms of schizophrenia, or many individuals with epilepsy. While significant progress has been made in treating relapsing and remitting forms of multiple sclerosis, there are no disease-modifying therapies for Alzheimer disease, Parkinson disease, or amyotrophic lateral sclerosis (Hyman 2014).

Major pharmaceutical companies recognize the large and growing prevalence of brain disorders as well as the vast unmet medical need. At the same time, they see no clear path to successful drug discovery and development with the significant exception of Alzheimer disease, where several companies are in the midst of clinical trials, all based on the beta amyloid hypothesis. Given the lack of knowledge of fundamental disease mechanisms for most common brain disorders, a dearth of new molecular targets, the failure of most current animal models to predict drug efficacy, and a lack of biomarkers, many companies have de-emphasized or abandoned efforts in brain disorders and have applied, instead, their resources to such areas as cancer and immune system disorders (Pankevich et al. 2014).

Paradoxically, just as industry has begun to abandon brain and nervous system disorders, breakthrough tools and technologies have emerged that are beginning to produce unprecedented insights into pathogenesis of brain diseases. Leaps in genomic and computational technology, resulting from the Human Genome Project, have yielded remarkable progress in genetically complex brain and nervous system disorders, including autism (De Rubeis et al. 2014), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014), and common forms of Alzheimer disease (Lambert et al. 2013). Findings from genetics studies are providing early insights into the molecular basis of these diseases, beginning to suggest new drug targets, and providing new hypotheses about potential biomarkers. The many hundreds of genetic loci that are emerging from genetics require relevant high throughput technologies to understand functional differences between alleles that confer disease risk and alleles of the same gene that do not. This has become possible over the last few years, with rapid development of methods to produce different neural cell types from stem cells, induced pluripotent cells, and directly from fibroblasts (Zhang et al. 2013). Different alleles can readily be engineered into and out of isogenic cell lines or patient-derived cell lines using genomic engineering tools (e.g., CRISPR) which have also emerged very recently.

These technologies have created the conditions for discovery and development of new drugs and therapeutic devices. However, because the technologies are new and results are at early stages, most companies are continuing their retreat from the brain, rather than incorporating new approaches. Indeed, approaches based on genetics differ greatly from prior drug discovery efforts for brain disorders—especially for neuropsychiatric disorders. In the past, much

drug discovery was grounded in pharmacology and animal behavior. When drug discovery efforts were based on genetic findings, they were limited to rare monogenic forms of illness with the hope that if useful results were forthcoming, they might prove generalizable. An important question is whether, and under what circumstances, industry would participate in drug discovery for polygenic human brain disorders.

"What is to be done?" was the motivational cry that spurred this Ernst Strüngmann Forum. Behind the mere simplicity of this question stands immense power and potential, as evidenced almost a century ago by another who posed the same question, and whose resulting thesis, Что делать, provided the world with a roadmap that led to a very different type of revolution (Lenin 1917/1990).

The emergence of high-quality neuroscience over the last decade combined with the disappointing state of clinical treatment presents a unique paradox. Although the term "paradigm shift" is overused, there is, at a minimum, a vast discontinuity between recent central nervous system drug discovery efforts and the implications for current science. To utilize the scientific approaches that are emerging, academic and industrial efforts must be better connected, with more effective interfaces between the various stakeholders involved in drug discovery and development (i.e., academia, funding agencies, patient groups, biotech and pharmaceutical companies, and regulatory bodies).

Oncology provides an example of what can happen: over the last 20–30 years, based on genetics—most importantly, many somatic mutations that contribute to a large number of cancers—and steady advances in genomics and molecular biology, it has been possible to develop drugs targeted to the effects of specific mutations and to stratify patients in a manner that matches them with the best current treatments. Although advances in oncology provide an important set of aspirations, it differs greatly from the study of brain disorders in that oncology research has direct access to diseased tissue and many of the molecular mechanisms of disease are cell autonomous. In contrast, the human brain can generally be examined only indirectly in life, and many disease processes affect many cell types and are expressed through dysfunction in widely distributed neural circuits. These challenges for neuroscience can only be overcome with great ingenuity, perhaps with greater reliance on human neurons *in vitro*, artificial circuits, and organoids, as well as advances in human experimental biology.

This Forum was thus convened to mobilize and energize the efforts of experts involved in translational neuroscience. It addressed the complexity of the brain and the associated challenges of connecting levels of analysis: from molecules to cells, synapses, circuits, and thence to higher cognition, emotion regulation, and executive function. It also sought to identify (a) tools to stratify patient populations, critical "driver" pathways, and circuits that cause disease in these stratified patient populations; (b) tools to map and modulate critical "driver" pathways and circuits; (c) reliable markers that can quickly

demonstrate target engagement and/or pathway modulation *in vivo* so that one can test and refine the hypothesis (and thus motivate a return to basic science); and (d) efficacy endpoints that do not require prohibitively long clinical trials. To do so, four working groups were formed to scrutinize the issues from the following perspectives:

1. *Neurodevelopmental disorders.* Heckers et al. (Chapter 4) begin by reviewing the current psychiatric classification of autism and schizophrenia, and show how this has impeded progress in understanding the underlying disease mechanisms of these disorders. They recommend that future research not be constrained by current nosology and explore alternative diagnostic approaches. Further, they review recent studies of prevention in the early stages of illness and the discovery of genetic and environmental risk factors. Both sets of observations can be used to guide future neuroscientific exploration of neurodevelopmental disorders unimpeded by current psychiatric nosology.
2. *Neurodegenerative diseases.* With the goal of developing more effective diagnostics and treatments over the next 5–20 years, Holtzman et al. (Chapter 7) identify areas where attention is needed to reveal a better understanding of these disorders: Major specific pathologies and circuit dysfunction in neurodegenerative diseases need to be identified during the life span along with dysfunctional circuits. In addition, genetically well-defined patient populations are likely to offer a better chance for therapeutic success. Therapies affecting neurotransmitter systems and signaling pathways should be further explored by utilizing defined patient populations and nodes of those affected by the disease. Better methods are needed to understand protein aggregation processes (from formation of misfolded proteins to the critical clearance pathways that regulate their levels and toxicity) as this could lead to novel therapeutics. A better understanding is needed of the role of apolipoprotein E (apoE), lipoproteins, and lipid biology under normal conditions as well as in neurodegenerative diseases. Attention must also be given to the blood-brain barrier, the neurovascular unit, and other barriers separating CNS from non-CNS compartments to facilitate both a better understanding of disease as well as drug/biological delivery. The role of the innate immune system and other immune mechanisms that contribute to progression of neurodegeneration remains to be elucidated. In addition, regardless of the upstream processes, it may be possible to activate neuroprotective mechanisms by defined factors, signaling pathways, or via cell-based methods. Given the current cost of these diseases to society and the expected increase in their prevalence, Holtzman et al. recommend that a major worldwide effort be put forth immediately and given the highest of priorities. With significant progress in each of these areas, they believe that substantial changes

could be made in the diagnosis and treatment of neurodegenerative diseases over the next twenty years.

3. *The pathophysiological toolkit: From genes to circuits*. Understanding the etiology and pathophysiology of neuropsychiatric disease requires the development of new tools, ranging from evolving diagnostic strategies to biomarkers of disease. Such tools must consider the unique challenges posed by neuropsychiatric disease, including the current lack of tractable interfaces between what can be learned in the clinic and the tools available using model systems in the laboratory. In their report, Dölen et al. (Chapter 10) outline some of these tools, addressing pitfalls and opportunities. They stress the importance of interfacing between model systems and acknowledge the iterative nature required to bridge the gaps between different levels of inquiry.
4. *Living systems: From models to patients*. Research tends to be done in a top-down or bottom-up manner, starting from symptoms or genes, respectively. While such unidirectional approaches work well in oncology and have the potential to advance understanding of monogenic neuropsychiatric diseases, successful application for complex, multifactorial disorders has resulted in a growing number of translational failures. Diester et al. (Chapter 13) investigate existing obstacles and explore options to overcome them. They find that it is essential to dissect complex diseases into measureable and manageable factors, which should then be investigated in a comparable and compatible assembly of model systems to test hypotheses, concepts, and ultimately drug candidates or other therapeutic interventions. Whereas some of these factors might be best investigated through a top-down approach, others might yield better results via a bottom-up approach. Both might be successful only up to a specific point in the experimental chain. Thus, Diester et al. consider it essential to define suitable bridging points between the two approaches, which they term a bidirectional approach. They stress that patients need to be included in this process, since disease-associated dysfunctions or symptoms are often behavioral in nature. In addition, to bridge behavioral readouts between models and humans, links to evolutionary conserved neural substrates need to be created. Some anchor points already exist that successfully bridge model systems to patients, and new promising ones (e.g., induced pluripotent stem cells) are emerging. Diester et al. argue that some recent developments could speed up translation of research into clinical applications (e.g., through faster drug screens in a patient-specific manner) and propose organizational structures that should permit faster transition from research to clinical applications. They also put forth the concept of a "third space" within which early proof of principle studies (Phase 0 and I) can be conducted more effectively.

As each group endeavored to identify existing "gaps" in knowledge and project potential solutions, it is important to note that consensus was not necessarily a goal. Ideas were pooled, as we sought to envision a conceptual roadmap that would create an effective, credible translational neuroscience leading from the patient to the lab and back again.

This volume sets forth the results of these collective efforts. It contains the state-of-the-art papers that served to ground our discussions as well as reports from each of the working groups (Chapters 4, 7, 10, and 13), which highlight, in particular, areas for future research. It concludes with the bold attempt to project the synergism that emerged into a concise conceptual roadmap. We hope that the ideas contained herein will fuel a radical change in translational neuroscience and initiate efforts to create new, effective therapies that will benefit the millions of people who suffer from the devastating impacts of brain and nervous system disorders.