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Ome's, ic's, and ip's: From the Bench to the Bedside and Back Again

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Two roads diverged in a wood, and I-I took the one less traveled by And that has
made all the difference

—Robert Frost, *The Road Not Taken* (1920)

The progress of science often seems to lead in one direction: forward (note how data “advance” a field). And yet, new hypotheses sometimes require a more circuitous path, one that connects past theories, often never proved inaccurate, with “new” data. Never before has the prevalence of mental illness, the fragmented mental health care system, and the lifelong negative impact of early life adversity been so evident. It is amidst this increased attention to mental health that the field of neurogenetics is rapidly evolving through directives such as President Obama’s Brain Initiative (<http://www.whitehouse.gov/share/brain-initiative>) and the National Institute of Mental Health’s (NIMH) Research Domain Criteria (RDoC) (<http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>). Against this backdrop of scientific advancement, it is perhaps the less traveled road, one that brings science back to the foundations of our field instead of away, that is the path to choose.

The thoughtful integration of neuroscience and genetics with child developmental theory will position psychiatrists to most effectively respond to NIMH Director Thomas Insel’s statement that “We are not doing well enough for our patients.” Amidst the recent decreases in deaths from cardiovascular disease, cancer, and the re-classification of human immunodeficiency virus as a chronic disease, suicide rates remain static. Psychiatric treatment modalities also remain static, and, for the most part, we remain unable to “cure” mental illness, as Insel reminded us at the Lawrence A. Stone, MD Plenary of the American Academy of Child and Adolescent Psychiatry’s 60th Annual Meeting in Orlando, FL, on October 25, 2013. The specialized developmental knowledge, unique trans-disciplinary skills, and the regular interaction with the diverse professions involved in the care of children who define the practice of child psychiatry are precisely the reasons why our field must orchestrate this integration.

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To better position child psychiatrists to lead this integration and to translate neuroscience for patients, families, and other professionals, “*ome*’s, *ic*’s, and *ip*’s” provide a common language describing where the science currently is and where it is heading. First, the “*ome*’s” of the *genome*, *proteome*, *epigenome*, *connectome*, *exposome*, and *brainnetome* offer increased precision about the molecular nature of psychiatric illness, holding the promise of assisting us in selecting the most effective psychotherapeutic and pharmacotherapeutic interventions. The power of a genome approach has been seen in other areas of medicine such as oncology, where the molecular phenotyping of cancer not only dramatically improved cure and remission rates, but also substantially decreased chemotherapeutic toxicity. Second, the “*ic*’s,” encompassing *synaptic*, *dendritic*, *plasticity*, *bioinformatic*, and *optogenetic* sciences provide clarity about the dynamic processes occurring in the developing brain and the critical impact of experience. Finally, the “*ips*” of *relationships*, *partnerships*, and *stewardships* provide the larger vehicles through which child psychiatrists can translate the *ome*’s and *ic*’s across disciplines and into practice.

The “*ome*’s”

The genome era has been one of great expectations. However, both geneticists and psychiatrists recognize that the genome has fallen short of its promise—particularly for psychiatric and non-psychiatric disorders in which the underlying genetic architecture is complex. The sequencing of the genome, albeit a significant scientific achievement, identified significant scientific gaps in our understanding of the molecular mechanisms regulating gene expression. Fully 98% of the genome does not code for proteins yet is critical for the higher-order regulation of gene expression found in the epigenome. The epigenome is influenced by development and the environment, as well as by their interaction. Epigenetic marks serve as a “record” of early experiences with implications across health outcomes. Yet, the epigenome and the proteome, the catalogue of proteins expressed in a given tissue or organism, are not distant concepts separate from the clinical realm. Psychiatry has long recognized the lasting impact of previous experiences and how these experiences influence treatment. The epigenome may simply be the molecular map of what our field has theorized for decades.

The “*ome*’s” have revolutionized the nature-versus-nurture debate, demonstrating the intricate and dynamic relationships between the environment, an individual’s genetic makeup, and experience. Large-scale ongoing research programs, such as the Brainnetome and the Connectome, expect to define normative neural developmental trajectories as well as the deviations that underlie psychopathology. Enhanced knowledge of the underlying circuitry will result in novel interventions but will also guide decisions related to when, during development, these interventions may be most effective. Beyond the direct clinical implications, patients now have the ability to access their own personalized genomic data (<https://www.23andme.com/>). Patients may soon bring genomic data with them to the clinic. Child psychiatrists will be expected to provide guidance about what genetics can and cannot tell them about risk, resilience, and vulnerability. This translation will require a new language, additional training for many, and new partnerships with genetic counseling and clinical geneticists to ensure accuracy. Thus the “*ome*’s” are a powerful set of tools that can

assist in defining the biological basis of mental illness, enhancing treatment outcomes, and guiding treatment selection (Table 1).¹

The “ic’s”

Neuroscience and psychiatry are intimately linked. Although psychiatric training extends beyond the brain to include the therapeutic alliance, transference, and relationship-building with our patients and their families, there is no doubt that mental illness originates in the brain. The “ic’s” (*synaptic, dendritic, plastic, bioinformatic, optogenetic*) have particular relevance for child psychiatry given that the developing brain, where synaptic connections are forming and strengthening, is also where most psychiatric illnesses originate (Table 2). Both preclinical animal models and human studies highlight the link between alterations in synaptic and dendritic connections and psychopathology, as well as the powerful effects of early life, including prenatal experiences, on neural architecture.² Neural plasticity, synaptogenesis, and dendritic arborization occur most rapidly during prenatal development and the first years of life, but also occur throughout the life course. These processes require time and are influenced by both the developmental stage and the cumulative environment. Even though the biology of neuronal connections may seem distant from our clinical work and theoretical foundation, these biological processes mirror what psychiatrists already know—that behavioral changes and enhanced emotional regulation skills require time, remodeling, and a multi-level approach. Advances in defining the molecular pathways controlling the opening and closing of sensitive periods and neural plasticity have direct, current bearing on both our psychotherapeutic approaches and the impact of the pharmacologic agents we use.^{3,4} Sensitive periods, as a construct, are very familiar to psychiatrists, who observe regularly the differential impact of treatments begun early in the course of an illness compared to the challenge of interventions initiated only after many years of illness.

Cutting-edge discoveries funded by NIMH such as optogenetics, a technological advance in which activation of a single neuron by light, *in a living animal*, now permit direct observation of the link between neuronal activation and actual behaviors. The CLARITY project (<http://www.nimh.nih.gov/news/science-news/2013/fat-free-see-through-brain-bares-all.shtml>), an innovative technology permitting the visualization of a 3-dimensional intact brain, from both animal models and postmortem human brains, provides never-before-possible information about the structural and molecular pathways of the brain. Enhanced bioinformatics, funded by the National Institutes of Health (NIH), creates the statistical platforms needed to manipulate these large data sets. NIH directives dictate free access to most data, making it feasible for clinicians and researchers to see the developing genetic and neuronal maps. Together these “ic’s” truly lay the foundation for substantial progress defining the developmental origins of psychopathology.

The “ip’s”

Neuroscience and genetics cannot replace the importance of relationships. Relationships with our patients, with their parents, and between children and their caregivers define our field. In addition to training in psychotherapies and medications, child psychiatrists

champion normal development while recognizing when deviations occur. Child psychiatrists also rely on partnerships. Among medical professionals, we have the greatest interaction with others focused on the care and development of children—pediatricians, teachers, coaches, principals, police officers, judges, public health officials, and public policy makers. Effective psychiatrists learn to navigate systems of care, schools, primary care practices, and myriad other environments. Therefore, child psychiatrists are best positioned to serve in a stewardship role for children, to safeguard society's greatest, yet most vulnerable, resource. The partnerships that child psychiatry must strengthen are clear: society, families, pediatricians, adult psychiatrists, public policy makers, public health officials, neuroscientists, and geneticists. This stewardship role must include partnerships with sometimes-controversial groups such as those in the pharmaceutical industry, as we strive to do everything possible to alter emerging psychopathology. Our role as stewards requires a new awareness, and perhaps a new image, as we build and strengthen these partnerships and bring our translation of neuroscience and its implications for child mental health to them.

Changing Our Image

To accomplish this translation, child psychiatrists need to expand our role beyond therapist and psychopharmacologist. Although newspapers daily identify a vast unmet need for child mental health services, child psychiatrists are often not heard, perhaps because our message is not conveyed clearly enough. By embracing neuroscience and genetics, we can establish that psychotherapies and pharmacotherapies do far more than decrease symptoms. Scientific evidence can demonstrate that these treatments reset neural pathways, the biological foundation of social–emotional development.⁵ Once we have begun down the road less traveled, where the fundamental theories of child psychiatry inform the translation of the science back to the clinic, child psychiatrists will have the greatest potential to improve the lives of children and their families.

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TABLE 1

The “*ome*’s”

<i>Genome</i>	The direct DNA sequence that is, for the most part, identical in each cell. Composed of 4 bases (ACGT), the genome is the main “instruction” for gene expression but also contains many non-gene elements that are linked to the epigenome
<i>Proteome</i>	The collection of proteins found within a given cell or tissue
<i>Epigenome</i>	The ever-increasing number of regulatory elements found “above” and around the genome that directly control gene expression in a cellular and developmentally specific manner. The epigenome includes methylation, histone acetylation and deacetylation, telomeres, chromatin structure, miRNA, and ncRNAs.
<i>Exposome</i>	The multi-level construct that reflects the cumulative exposure of individuals to their environment. This includes traditional measures of adversity such as abuse and neglect but goes beyond those constructs and includes chemical and environmental factors, school and home ecology, diet, exercise, and other life experiences such as community-level adversity and buffers. The exposome is perhaps most closely linked with what child psychiatry has compiled routinely as part of our biopsychosocial construct, although now with a new name. http://www.cdc.gov/niosh/topics/exposome/
<i>Connectome</i>	The U.S.-based effort to map the adult brain at the level of individual neuronal connections. The National Institutes of Health (NIH)–funded effort will provide free access to all data and an unprecedented opportunity for researchers to get at the basis of the altered neural circuits that are 1 component of psychopathology. (http://www.humanconnectomeproject.org/).
<i>Brainnetome</i>	A correlated effort by China to determine from cells to the whole brain how molecular changes affect cells, neural connections, brain regions, and behaviors and cognitive function. (http://www.brainnetome.org/en/)

TABLE 2

The “*ic*’s”

Synaptic	Increasingly, it is recognized that fundamental to psychopathology are altered connections, or synapses, between neurons. As we better define the molecular mechanisms controlling synapse formation, and the developmental corollary of pruning whereby unused connections are removed, we gain much-needed insight to guide the development of novel treatment modalities, including pharmacological agents and also non-pharmacological agents such as transcranial magnetic stimulation (TMS).
Dendritic	The branches of a neuron that are required for the development and strengthening of neuronal circuits. Dendritic arborization, i.e., the increasing complexity of these branches, is a critical part of brain development and maturation influenced by experience. Translational animal models of early adversity and stress have identified altered dendritic formation in the hippocampus and other brain regions.
Plastic	Neural plasticity is the changes in neural pathways and connections in the brain as a result of development, injury, and the environment. It is the neurobiological mechanism by which experience, both positive and negative, shapes the developing brain. Windows of increased plasticity during development and potentially throughout the life course may exist and represent periods of heightened sensitivity to change, both positive and negative. Altering plasticity and sensitive periods remains not only an active area of research with significant implications for child psychiatry, but also with significant caveats and concerns.
Bioinformatic	The interdisciplinary field that has developed to manage large-scale databases. The National Institutes of Health (NIH) continues to build and to support the public accessibility of raw and processed data generated by studies that they support, including expression studies of the brain and genome-wide studies. (http://www.brainspan.org/ and http://www.ncbi.nlm.nih.gov/)
Optogenetic	One of many novel investigative approaches supported by the National Institute of Mental Health (NIMH) to provide insight into neuronal connections, in vivo. (http://www.stanford.edu/group/dlab/optogenetics/)