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Editorial

Editorial for "What can clinical findings tell us about the neurobiology of schizophrenia? Revisited"☆

In 2013, we asked the question: what can clinical findings teach us about the neurobiology of schizophrenia? In response to that, we assembled a special issue on schizophrenia in Neurobiology of Disease (Sakurai et al., 2013). For the past 5 years, we have witnessed tremendous progress in psychiatric research, not only limited to schizophrenia. First, the excitement of the "gene hunting" era on the basis of genome-wide association study is nearing the end with a landmark paper that defines major susceptibility loci in the human genome for schizophrenia (Marshall et al., 2017; Pardinas et al., 2018), and we are transitioning into a post-genomic era when we are expected how to use "descriptive" data from psychiatric genetics under the challenge of very small effect size of each risk gene (Delevich et al., 2017). Second, with help from the Brain Initiative, both clinical and basic brain science has taken advantage of having new technology that enables us to trace specific circuitries in the brain in a fine detailed and comprehensive manner, which is now reflected in an amazing advance in human brain imaging *e.g.*, (Demirtas et al., 2019). Furthermore, we can now modulate those specific circuitries using optogenetic and pharmacogenetic intervention strategies (Kim et al., 2017). These technical advances have aided in elucidating many circuitries and brain regions important for certain brain functions. Third, related to the above two, "big data" science has become available in neuroscience and psychiatry: for example, human brain imaging data from multiple institutions are integrated and applied to a deep learning algorism for translational utility (Viviano et al., 2018). Fourth, instead of standing on classic diagnostic classification that maximizes clinical utility and reliability by sacrificing etiological and biological validity, researchers have paid more attention to stratify patient groups by biologically-valid, sometime cross-diagnostic, constructs in which biological factors at molecular, cellular, and circuitry levels can account for each clinical and behavioral manifestation in a logical manner (Owen et al., 2016). In contrast to the former (categorical approach), the latter (dimensional approach) has been emphasized as an effective approach to understand brain disorders, which matches with the general concept of "precision medicine" (Owen et al., 2016). The NIMH-proposed Research Domain Criteria (R-DoC) is a reflection of such efforts (Sanislow et al., 2019). Fifth, in addition to dissecting psychiatric conditions in a cross-sectional manner, researchers have realized the significance in paying attention to developmental trajectory for psychiatric disorders. In summary, the key phrases of major advancement in psychiatric research for the past 5 years may be (1) emergence of the post-genome era, (2) technological advance to visualize and intervene with the brain, in particular the advance in human brain imaging, (3) introduction of "big data" science, (4) dimensional approach, and (5) pathological trajectory in brain development. Based on this understanding, we arrange a special issue for neurobiology of schizophrenia in 2019 to provide a novel showcase of excellent research in the post-genome era with the following 10 articles.

We first introduce 4 papers that stand their research on clinical observations. Advances in human brain imaging have directly supported research that addresses important clinical questions. Heterogeneity of treatment outcomes in schizophrenia is an important clinical question, which may be associated with individual differences in its pathology. Nucifora et al., 2019 reviewed clinical, neuroimaging, and neurobiological characteristics of treatment refractory schizophrenia and suggested an idea of a biologically distinct group under the diagnosis of schizophrenia. Tarcijonas and Sarpal, 2019 extended this discussion and provided evidence how brain imaging, in particular MRI, may be a promising tool to estimate the outcomes of treatment. Furthermore, Coughlin et al., 2019 discussed the utilization of PET neuroimaging, by which the authors suggested a tool in guiding better treatment. These are certainly many examples for the path towards precision medicine in psychiatry. Miyata, 2019 proposed an integrative approach to understand salience as a fundamental feature of psychosis. Here large sets of data in brain imaging and neuropsychology are integrated by using computational methodologies. All these clearly demonstrate that clinically important questions are now addressable at least at the descriptive levels by directly analyzing humans.

Nevertheless, if we wish to address fine mechanisms of the pathology, experimental models are still very important. The next 3 papers will introduce this aspect. First, postmortem brains have been useful to pinpoint which brain areas and which cells are impaired in the pathology: Dienel and Lewis, 2019 discussed alterations in cortical interneurons and cognitive functions in schizophrenia. Since we detect the network alterations in human brains at least at the descriptive levels, it is important to connect such gross observations with molecular and cellular mechanisms. The study of postmortem brains provides this opportunity. Analyzing cells/tissue derived from humans have been challenging, but even in this area, there has been tremendous progress in the past 5 years. iPSC technology and 3D organoids derived from human iPSC made it possible to have access to human neuronal cells for characterizing cellular phenotypes, which is critical for understanding individual vulnerability associated with the disease and may be an initial step for screening of new compounds for drug discovery. Balan et al., 2019 overviewed the recent progress in the field. Finally, even with the many available ways of studying human biology, animal models are still useful in addressing fine network and molecular

☆ Schizophrenia research in 2019: Are we really making progress?

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mechanisms. Kimoto et al., 2019 discussed neurobiology and treatment of social cognition in schizophrenia, both in animal studies and human studies.

Both genetic and environmental factors define individual vulnerability to the disease in the developmental trajectory. Kaufman and Torbey, 2019 summarized and discussed child maltreatment as a critical risk factor for psychosis. Such adverse events in early development may be imprinted at the biological level, which in turn influences the onset and symptoms of schizophrenia. Sakurai and Gamo, 2019 discussed development of cognitive functions associated with the prefrontal cortex during adolescence, which is another crucial time period for progression of schizophrenia. Kelly et al., 2019 overviewed neural correlates of cognitive deficits across developmental phases of the disorder: the authors showed that most cognitive domains are affected across the developmental trajectory with corresponding structural and functional differences in the brain. They also discuss vulnerability in circuitries in the developing brain that may be further damaged during adolescence. All these papers stress the importance of forward and back translation between animal and human studies, with a clear idea on what can be modeled and what cannot be modeled.

It has been an amazing 5 year period in that we have come all this way in the study of brain disorders, and in many cases directly tackling human brains (human biology). We still have many questions, but it is fascinating to imagine how far we will go in this endeavor towards the eventual better treatment for this debilitating disorder in the next 5 years. Finally, we wish to note the late Dr. Larry Seidman (cover page). During preparation of the special issue, Larry was one of the first colleagues to discuss the plan. He also agreed to write one chapter. We are greatly saddened by the loss of Dr. Larry Seidman. It came too suddenly. Larry was a great researcher, great clinician in psychology, great teacher, and…even more impressively, an outstanding tennis player (see picture below, provided by As).

In sum, he was a great person and indeed a senior friend of ours. We would like to dedicate this special issue to Larry, with permission from all contributors.

We would like to thank Dr. Marcheri S Keshavan at Harvard Medical School for sharing his thought on late Dr. Seidman and providing us with his picture for cover page.

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