Multifaceted Translational Approach to Major Mental Illness

Akira Sawa

Abstract This is a short summary of my presentation in the Uehara Memorial Foundation Symposium 2014. Classification of mental illness in current diagnostic systems [such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)] is built on clinical reliability and utility, but not on etiological validity. Thus, the DSM has not provided an ideal classification of mental disorders. To overcome the dilemma, the National Institute of Mental Health (NIMH) recently proposed the Research Domain Criteria (RDoC) framework. This new framework emphasizes a dimensional approach on the basis of neurocircuitry mechanism. There were three aims in my presentation. First, I summarized the concept of research strategies on the basis of dimensional approach, with a link to the trajectory from early development to adolescence in the disease pathology. Second, I introduced an example of a research infrastructure that could support translational and clinical study for mental illness. Third, I showed two studies that were utilizing the infrastructure.

Keywords Mental disorders • Diagnostic and statistical manual of mental disorders (DSM) • Research domain criteria (RDoC) • Dimensional approach • Developmental trajectory • Translational research

Introduction

The Uehara Memorial Foundation Symposium 2014 was held on June 15, 16, and 17 in Tokyo, under the theme of Innovative Medicine—Basic Research and Development. The role of my presentation was to provide information on the frontline of clinical and translational research in psychiatry to the audience.

Although psychiatry is obviously a domain of modern medicine, studying brain disorders, the classic problem of the brain–mind discontinuity has slowed down scientific progress in psychiatry. Consequently, many different disciplines have

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competed with each other in psychiatry in the past century. Such factionalism was also a major obstacle to the development of psychiatry as a key domain of modern medicine. Finally, as a major collaborative effort among psychiatrists, a comprehensive diagnostic manual that standardizes the classification of psychiatric disorders was issued as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) third edition in 1980. The DSM has been useful in standardizing clinical practice in psychiatry with high reliability. However, the DSM has been formulated under ignorance of (or minimal attention to) the etiological and biological validity in its disease classification. Thus, this nature of the DSM has been a major deficit in building research on the basis of disease classification defined by this manual.

To overcome this dilemma, the National Institute of Mental Health (NIMH) included in its new strategic plan the following aim: "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [1]. According to the Cuthbert article, "the implementation of this aim was named the Research Domain Criteria project or RDoC." The RDoC is formulated in a matrix: it has multiple dimensions that cut across traditional diagnostic categories, such as attention and perception. Meanwhile, biological correlates for each dimension are considered at multiple levels, such as the molecular, cellular, circuitry, and behavioral levels.

There is another important viewpoint to develop research for mental illness. This is the viewpoint of the developmental trajectory. Many mental disorders, such as schizophrenia and psychotic disorders, mood disorders, and substance use disorders, appear in young adulthood, and epidemiological and clinical studies have indicated that major risks for such disorders occur in developmental stages. Thus, it is very important to study the mechanisms of how disease-associated risk factors at earlier ages are accumulated and result in the onset of the disease in the developmental trajectory. The NIMH has also stated that dimensional approaches such as the RDoC may be used in conjunction with attention to neurodevelopment and disease-associated environmental factors.

Thus, the aim of my presentation in the symposium was to introduce these two elements essential to research for mental disorders (e.g., a dimensional approach and attention to the neurodevelopmental trajectory in disease pathology), and then to present a representative infrastructure of translational and clinical research on the based on these two elements.

Major Mental Illness Caused by a Combination of Multiple Genetic Risk Factors and Environmental Stressors in the Pathological Trajectory

The majority of mental disorders are caused by a combination of multiple genetic risk factors and environmental stressors (Fig. 1). The combination is not random but is likely to result in certain numbers of common biological pathways. It is possible that these pathways underlie clinical manifestations, which are organized in a

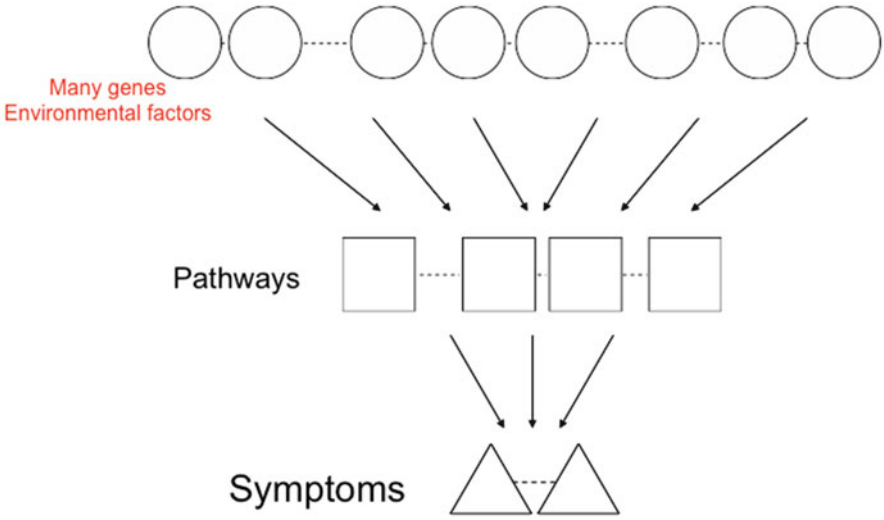

Fig. 1 From etiologies to clinical manifestations: the majority of mental disorders are caused by a combination of multiple genetic risk factors and environmental stressors

dimensional way. If we take schizophrenia (SZ) and related psychotic conditions, the risk factors and stressors are likely to contribute to the pathology in early development and adolescence (Fig. 2). Nonetheless, the onset of the disease is in late adolescence and young adulthood. Thus, it is crucial to study the disease mechanisms in the developmental trajectory. In many medical diseases, the significance of early detection and early intervention has been highlighted. Accordingly, in the case of SZ, studying the transition from risk stages to the onset (the prodromal stage) is regarded as one of the most important research topics at present. Given that current medications for psychosis target only symptomatic aspects and are limited in their efficacy, many investigators optimistically expect that the study of the prodromal stage may identify novel therapeutic targets that are associated with the disease progression and overcome the current limitations (Fig. 2). In regard to the mechanisms associated with the disease progression in the prodromal stage, it is possible that aberrant activation of stress-related cascades underlie disturbed postnatal brain maturation, which results in brain dysfunction and manifestation of mental symptoms (Fig. 3) [2, 3].

Research Infrastructure That Allows a Multifaceted Translational Approach to Major Mental Illness

After the introduction of the dimensional approach in the developmental trajectory, particularly in the context of SZ and psychotic conditions, I presented an example of a research infrastructure that supports translational and clinical study for mental

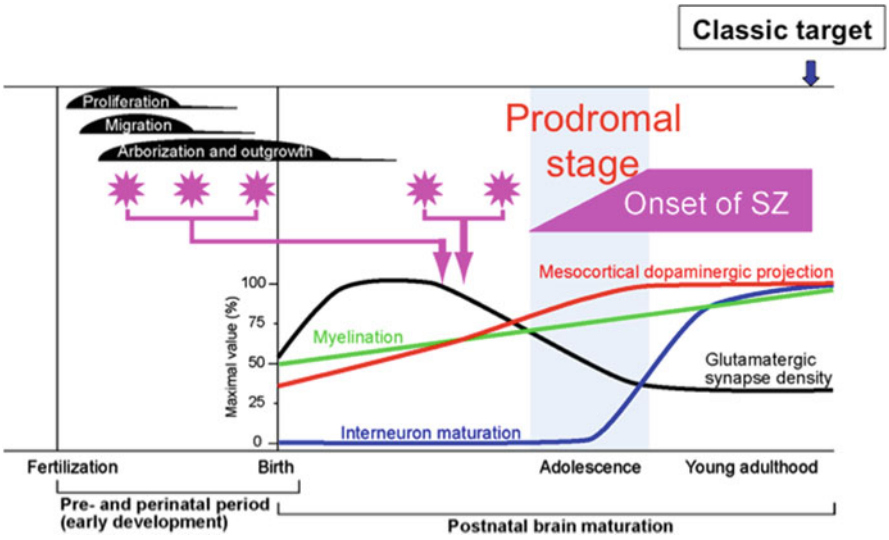

Fig. 2 Developmental trajectory of schizophrenia and related psychotic conditions. Although the onset of SZ is in young adulthood, epidemiological studies have suggested that many environmental risk insults for SZ occur during early development and adolescence (*asterisks*). Biological studies have also provided evidence that roles for genetic risk factors are associated with neurodevelopment (Adopted and modified from Jaaro-Peled et al. [2])

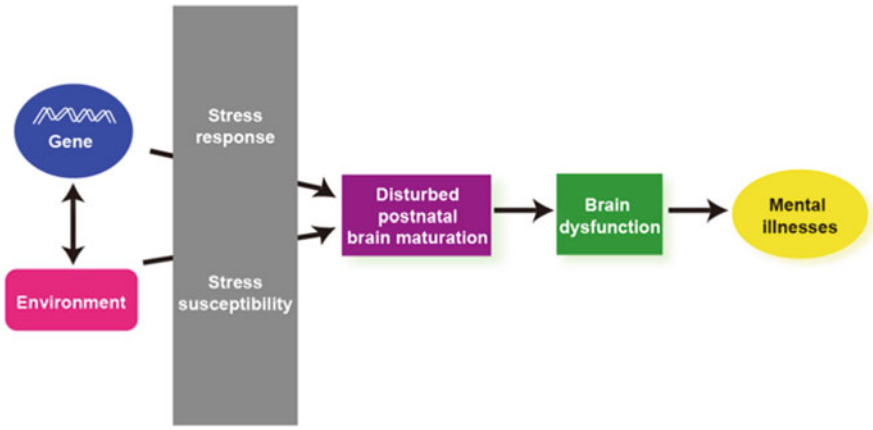

Fig. 3 Gene environmental interactions that underlie disturbed postnatal brain maturation, brain dysfunction, and mental disorders. Genetic and environmental factors for SZ are likely to converge and affect proper cortical maturation in adolescence, which may underlie the pathology of SZ

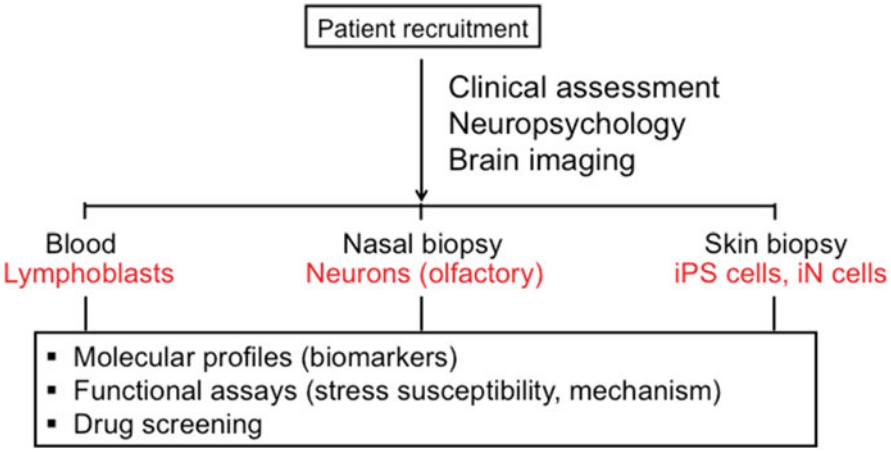

Fig. 4 An example of research infrastructure that supports translational and clinical study for mental disorders. In this infrastructure, whenever study subjects (patients and matched controls) are enrolled, they are assessed clinically and neuropsychologically. They also participate in brain imaging studies as well as tissue biopsies. Taken together, according to the ethical guideline, investigators can build multifaceted translational study on this research platform

disorders (Fig. 4). In this infrastructure, whenever study subjects (patients and matched controls) are enrolled, they are assessed clinically and neuropsychologically. They also participate in brain imaging studies, including positron emission tomography (PET) and magnetic resonance imaging (MRI), which are essential to address brain circuitry disturbance directly in vivo. In parallel, the study participants donate their tissues in multiple ways, including blood draw, skin biopsy, and nasal biopsy. We can obtain an olfactory epithelium (OE) sample easily by nasal biopsy. OE includes neuroprogenitor cells, immature neurons, and mature neurons: thus, by studying OE-derived cells and tissues, we can examine molecular and cellular signatures relevant to neuronal cells (Fig. 5) [4]. The information from the cells and tissues can be correlated with the brain imaging characteristics and clinical manifestations from the same subjects. As described above, RDoC-oriented studies are expected to study biological correlates and clinical manifestations at multiple levels, such as the molecular, cellular, circuitry, and behavioral levels. Thus, this infrastructure can meet such expectations. The disease trajectory may be addressed by designing a longitudinal study in this infrastructure.

Two Representative Studies that Use the Research Infrastructure

We previously reported that a specific phosphorylation of DISC1 (serine residue at the 710th amino acid of mouse DISC1) has a crucial role in the switch of cell fate from neuroprogenitor proliferation to postmitotic differentiation [5]. DISC1 has

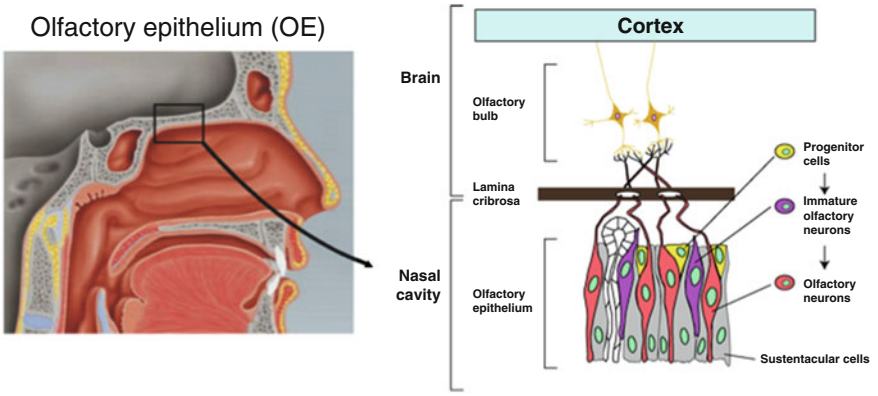

Fig. 5 Olfactory biopsy as a effective approach to obtain biospecimens with neuronal molecular signature. An olfactory epithelium (OE) sample, which is easily obtained by nasal biopsy, includes neuroprogenitor cells, immature neurons, and mature neurons; thus, by studying OE-derived cells and tissues, we can examine molecular and cellular signatures relevant to neuronal cells (Adopted from Sawa and Cascella [4])

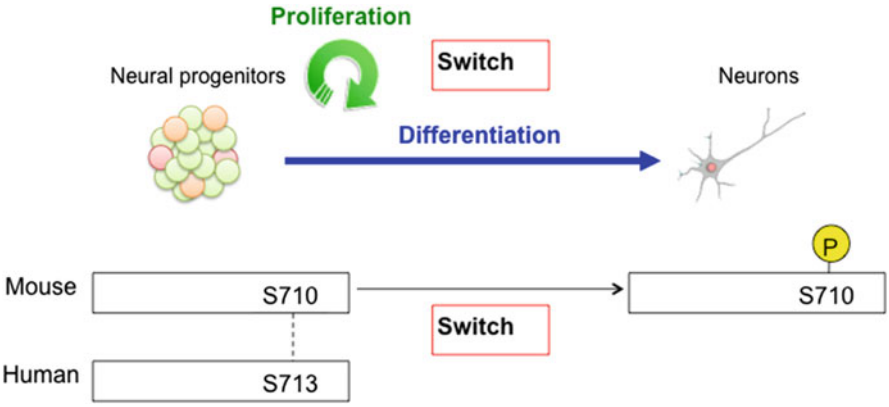

Fig. 6 A specific phosphorylation of DISC1 controls cell fate from neuroprogenitor proliferation to postmitotic neuronal differentiation: an entry point for translational study of mental illness. DISC1 has been involved as a biological hub protein for multiple pathways associated with mental illnesses. Phosphorylation of DISC1 at one specific amino acid residue is known to be crucial for neurodevelopment in mice. However, it remains elusive how this phosphorylation (serine residue at 713th amino acid of human DISC1) underlies cellular, circuitry, and behavioral manifestations associated with mental disorders. The infrastructure introduced in Fig. 4, including the utilization of olfactory cells (see Fig. 5) for study of the phosphorylation, allows us to address this question

been involved as a biological hub protein for multiple pathways associated with mental illnesses [6]. It remains elusive how this phosphorylation (serine residue at the 713th amino acid of human DISC1) underlies cellular, circuitry, and behavioral manifestations associated with mental disorders (Fig. 6). Thus, I presented our

preliminary data that studied the phosphorylation in olfactory cells from patients and controls, in correlation with their brain imaging characteristics and clinical traits.

In addition, I also presented studies in which the molecular signature of the cerebrospinal fluid was examined from patients in the prodromal stage and with the first episode of psychosis, in comparison with matched controls. In the first set of publications from the study, we observed robust changes in the molecules associated with immune and inflammatory responses, as well as oxidative stress [7, 8]. I also introduced a perspective of how we can study such molecular information in correlation with brain imaging characteristics and clinical manifestations.

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