

Review

Behavior, cognition, and future direction of psychiatry

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Abstract

The human behavior and cognition are the two most important functions for human life in the society. The cognitive function is declined in the elderly, but it is not always the case. Fluid intelligence may decline along with aging but crystalized intelligence can be maintained even in the elderly.

In addition to neurocognitive disorders (dementia), cognitive function is impaired with various psychiatric disorders and it will be the main target for future psychiatry. Due to the knowledge obtained from the recent development in brain mapping, psychiatrists can perceive and understand the meaning of the psychiatric symptoms based upon the dysfunction of these networks. Subjective experience of the patients should be paid more attention by closer collaboration between psychiatrists/ researchers and patients/ families.

Elucidating the brain network representing common sense will be important. Psychiatrists are recommended to expand the range of the frame of their common sense to be able to understand the meaning of the patient behavior.

Key words: psychiatry, behavior, cognition, common sense, brain network

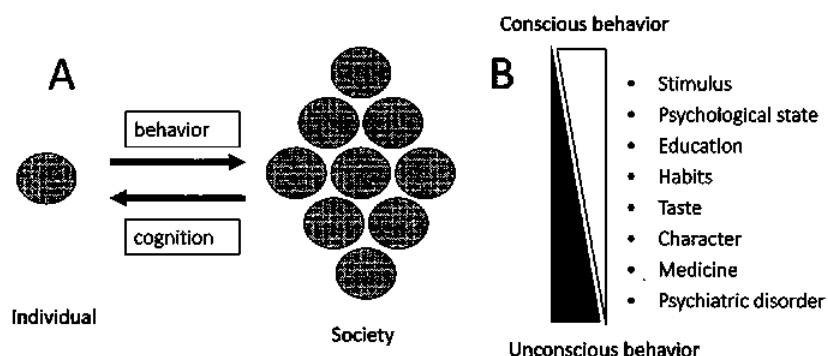
The human beings have evolved the central nervous system (CNS) and the immune system to produce the optimal behavior or response to the stimuli from outside world to incorporate environmental factors to their life. The CNS defines our behavior to outside stimuli, and the immune system regulates the appropriate biological response of the organ to ambient conditions.

Psychiatry is a discipline of medicine mainly dealing with abnormal behavior of human subjects, and action and behavior of the subject is produced and modulated by the CNS responding to various factors. In the CNS, the substances of various levels (gene, protein, cell, tissue, or organ) are involved with the process of behavior production which is finely modulated by the crosstalk among neurotransmitters, hormones, and cytokines. To understand the mechanism of

abnormal behavior of human beings, psychiatrists need to integrate the knowledge on various biological, psychological and social factors. Therefore, we believe that multilayered psychopathology is essential in psychiatry

Humans engage social life utilizing behavior as the currency

Abnormal behavior of subject is the primary target of psychiatry. Humans live in the society producing various behaviors, and the behavior itself functions in the society just as the currency does. Humans choose the appropriate behavior by recognizing the stimuli from the outside world, and cognition and behavior of the subject are functioning as the currency in social life, responding each other (Fig. 1).



A. Human behavior and cognition. Humans live in the society using behavior as the currency does in the society. An individual perceives the stimuli from the outside world by cognitive function, which is utilized to modulate behavior responding to the society.
 B. Modulation of human behavior by conscious and unconscious factors. Human behavior is modulated by the combination of conscious and unconscious factors. The typical conscious behavior is produced responding to the stimuli from the outside world. The response to the stimuli is also modulated by the psychological state, education, habits, or taste of the individual. Of course, the character of the individual affects the content of the behavior. Further, medicine acting to the CNS or psychiatric disorders significantly affects the behavior of the individual.

Fig. 1

Human behavior is sometimes unconsciously performed. For example, the reaction to the stimuli from the world outside can be modulated by psychological state of the subject, often showing different reactions to the same stimuli. Even if the external stimulus is the same, humans may show different behavior depending on the level of education, the contents of the past experience, habits, taste, or personality of the subject. Such volitional behaviors are primarily performed on the conscious level, but it is not usually perceived subjectively that the behavior is influenced by unconscious factors.

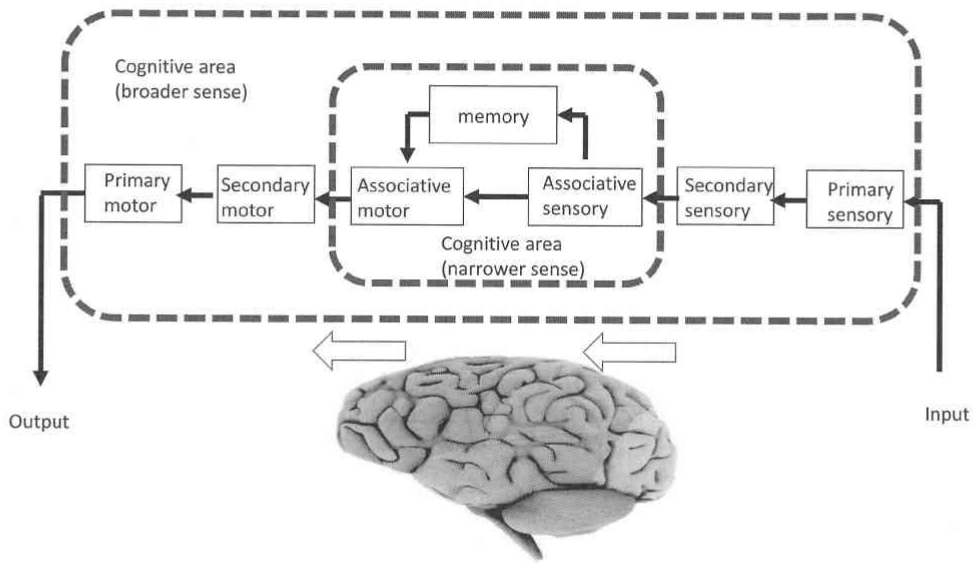
Drugs acting on the CNS should also be mentioned as a possible factor with significant impact on the behavior and cognition. Psychiatric disorder also causes significant changes in the behavior which might be caused by the change in cognition, resulting in the specific set of behavioral patterns unique to each psychiatric disorder. Abnormal behavior is a direct target of psychiatry, and cognitive function is also the one at the same token.

Definition of cognitive function

Cognition can be defined in broader or narrower senses depending on the context. Generally speaking, it can be defined as the function to choose the appropriate human behavior corresponding to the stimuli and information from outside. In other words, the cognitive function may collectively include all intellectual function of humans including language, calculation, memory, learning, and problem-solving. The input information from outside is accepted by the

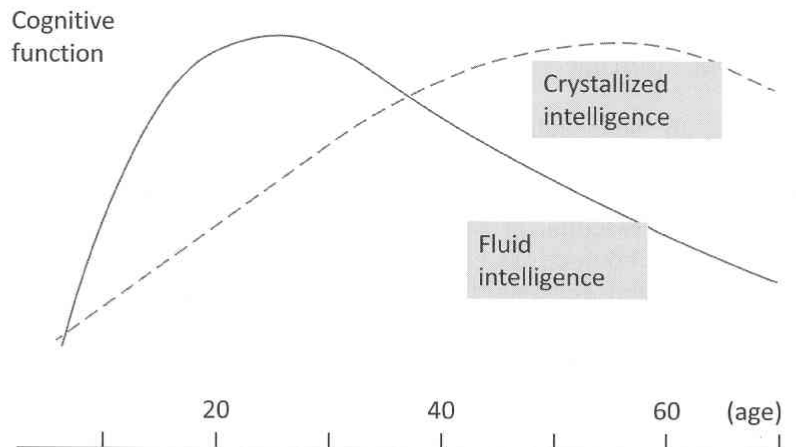
primary sensory cortex of the brain, delivered to the secondary sensory cortex, and finally to the associated sensory cortex where the information from outside is processed to produce the most appropriate behavior. The processed information in the association cortex is collated with the information stored inside the limbic system of the brain, and the output is firstly determined in the association motor cortex, then delivered to the primary motor cortex through the secondary motor cortex. The information processing in the brain, flowing from the rear to the front of the cerebrum, is the core process of the cognitive function. In narrower meaning, the cognitive function is carried out in the association sensory, association motor and memory area of the brain. In case of broader meaning, however, the cognitive function might also refer to the entire cerebral cortex. In general, the cognitive function can represent function of the higher brain function such as memory, learning, language, and executive function (Fig. 2).

Cognitive impairment is defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorder (DSM-4)* as the dysfunction in either one or more domains of cognitive function: memory impairment, aphasia, apraxia, or executive dysfunction. In *DSM-5*, six domains of cognitive function are listed: (complex) attention, executive function, memory and learning, language, perceptual-motor, as well as social cognition. Neurocognitive disorder is defined as the impairment in one or more domains of cognitive function in *DSM-5*.



The input into the primary sensory area is transferred to the association sensory area through processing in the secondary sensory area. The output is produced in the association motor area in which the information is correlated with that in the limbic system (memory area). The output is processed in the secondary motor, and finally in the primary motor area, the actual response, action, or behavior is put forward to outside of the brain.

Fig. 2 Cognitive function



Cognitive function can be classified into two categories: fluid and crystallized intelligence. Fluid intelligence is gradually declined in the elderly. Crystallized intelligence, however, is maintained in the elderly

Fig. 3 Fluid intelligence and crystallized intelligence

Aging and cognitive function

Generally speaking, cognitive function has been believed to decline with age in the elderly. It is not the case, however, every domain of cognitive function declines at the similar rate. Some domain of cognitive function can be preserved even in the elderly. Cognitive function that is evaluated traditionally as intelligence quotient (IQ) in the field of experimental psychology, is commonly divided into the two categories: fluid intelligence and crystallized intelligence. Fluid intelligence such as simple memory, and working memory, is subject to decline by aging in the elderly. But

crystallized intelligence such as common sense, reasoning, or judgment, is maintained even in the elderly. As shown in Fig. 3, some of the crystallized intelligence can be improved even in the elderly.

Successful aging

Humans are born as a baby that is similar to each other with little individual difference. Along with the life of humans through the staging of child, adolescence, adult and the elderly, education and experience are accumulated in life, resulting

in significant individual differences in the elderly. The elderly show the widest range of individual difference, not only in physical ability, intellectual ability, or economic capacity, but also in social competence.

The World Health Organization (WHO) has proposed the term of “aging society” to the society with 7% or more elderly 65 years old and above. The society with 14% and more of the elderly is called “aged society”. The society with 21% or more of the elderly can be called “super-aged society”. There has been lots of discussions on which life style is suitable for the elderly living in aged or super-aged society. Since significant difference exists in capacity of the elderly, the simple dichotomy between normal and abnormal is not enough to describe the life capacity of the elderly life. The concept of “successful aging”, “active aging,” or “creative aging” is often discussed because the simple dichotomy is misleading. Given the diversity of the individual difference in capacity of the elderly, the simple dichotomy, normal or diseased, is insufficient. Rather it is advisable to consider the elderly in the spectrum from “normal aging” through “successful aging.”

We had better describe an elder individual, placing a person to a certain point in the spectrum considering individual difference in the actual situation. Cognitive function is essential in the daily life of the elderly. In this context, an extreme example of unsuccessful aging is dementia.

In order to achieve the successful aging the following four conditions are required: (a) physical

health, (b) normal cognitive function, (c) life satisfaction and happiness, as well as (d) social activities and social productivity. Above all, maintaining the normal cognitive function is important to successful aging. As shown in Fig. 4, the interrelationship among normal cognitive function, life satisfaction and social activity have been previously discussed (Takeda et al. 2015).

Cognitive decline due to neurocognitive disorders

In *DSM-5*, neurocognitive disorder has been proposed, which has a slightly broader meaning than dementia. As depicted in Fig. 5, the schema of cognitive decline due to neurocognitive disorder include the mild cognitive impairment (MCI) and subjective cognitive impairment (SCI) as the stage preceding dementia when social life, personal life and biological life capacities can be preserved. In dementia, personal life capacity in addition to social life capacity is impaired, while biological life capacity such as breathing, cardiac circulation, and other functions is preserved, required for humans to live biologically.

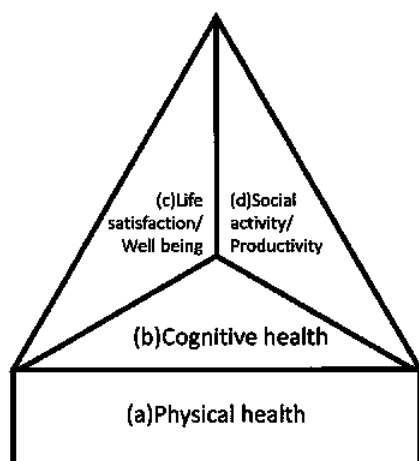
In mild cognitive impairment (MCI) as a pre-stage of dementia, only social life capacity is impaired while the capacity for both personal life and biological life capacity is maintained. Before MCI, there is a stage of subjective cognitive impairment (SCI) in which memory function is slightly impaired compared with that in 30s of the individual. The complaint is mainly subjective, but full capacity in social life, personal life and biological life is maintained (Fig. 5)

Cognitive impairment due to psychiatric disorders

Cognitive dysfunction is observed as the foreground symptom in neurocognitive disorders by definition. Dysfunction in cognition is, however, also observed in a number of psychiatric disorders other than dementia. Cognitive impairment of psychiatric disorders has been attracting more attention as the core symptoms of the disorders.

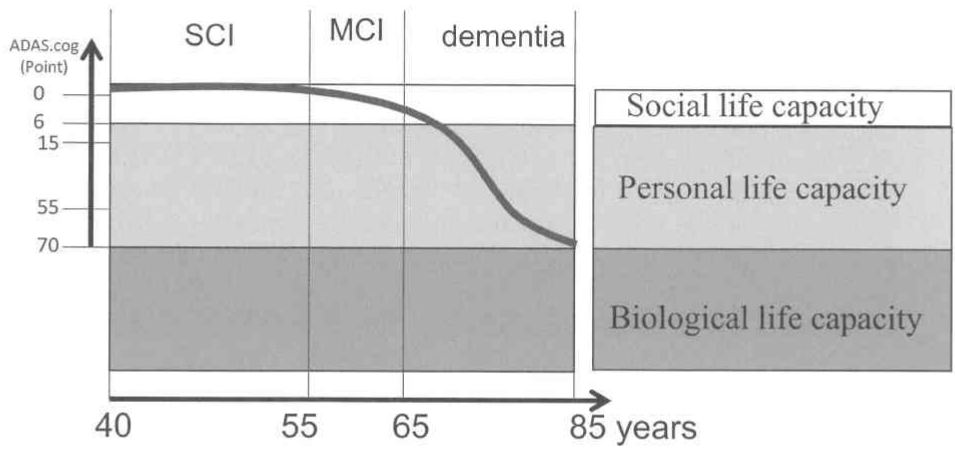
In Fig. 6, the cognitive dysfunction in schizophrenia is listed. Schizophrenia patients show severe dysfunction in verbal memory, executive function, alertness, and word fluency, dropped below 2-3 standard deviations (SDs) compared with the healthy control. On the other hands, the patients maintain the full capacity of word reading and word understanding, and long-term episodic memory (Fig. 6).

Cognitive capacity of the patients with major depression, anxiety disorder, and bipolar disorders is shown in Fig. 7. Psychiatric patients all



(a) physical health, (b) normal cognitive function, (c) life satisfaction and happiness, and (d) social activities and social productivity are required for the successful aging. Above the physical health, cognitive health is the most important to attain successful aging. (b) normal cognitive function, (c) life satisfaction and happiness, and (d) social activities and social productivity are interrelated each other.

Fig. 4 Successful aging



SCI: subjective cognitive impairment MCI: mild cognitive impairment
 In subjective cognitive impairment (SCI), social life, personal life and biological life capacity is preserved. In mild cognitive impairment (MCI), social life capacity is impaired but personal life and biological life capacity is preserved. In dementia stage, social life and personal life capacity are significantly impaired, but biological life capacity is preserved.

Fig. 5 Cognitive decline and life capacity.

Severe impairment*	intermediate impairment**	slight impairment***	no impairment
Verbal memory Executive function Arousal Word fluency	transductivity delayed recall visual motor capacity of immediate memory verbal IQ working memory	perception skill delayed recall naming	reading and meaning of words long term episodic memory

Severe impairment (*) implies the mean value is 2-3 SD below than the control with matched age and education. Intermediate impairment (**) implies 1-2 SD below than the control, and slight impairment (***) implies 0.5-1.0 SD below the control. (Roitmsan, Harvey, Keefe, 1997)

Fig. 6 Cognitive impairment with schizophrenia

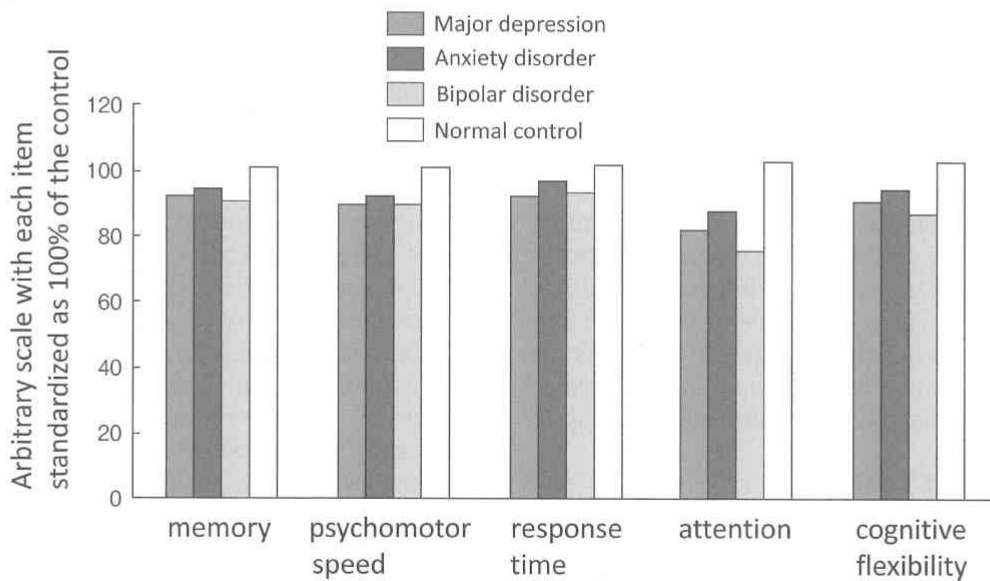


Fig. 7 Cognitive impairment with major depression, anxiety disorder, and bipolar disorder (Gorwood et al, 2008)

number of domains with less than 70 points	major depression	anxiety disorder	bipolar disorder	normal control
0	61.4	60.3	57.3	89.1
1	17.9	20.6	12.5	7.3
2	9.1	12.7	13.5	2.6
3	5.6	3.2	6.3	1
4	3.9	3.2	6.3	0
5	2.1	.	4.2	0
2 to 5	20.7	19	30.2	3.6

Fig. 8 Number of domains showing below 2 standard deviations (less than 70 points) by category of disorder
(Gorwood P, Corruble E, Falissard B, Goodwin GM. Am J Psychiatry. 2008)

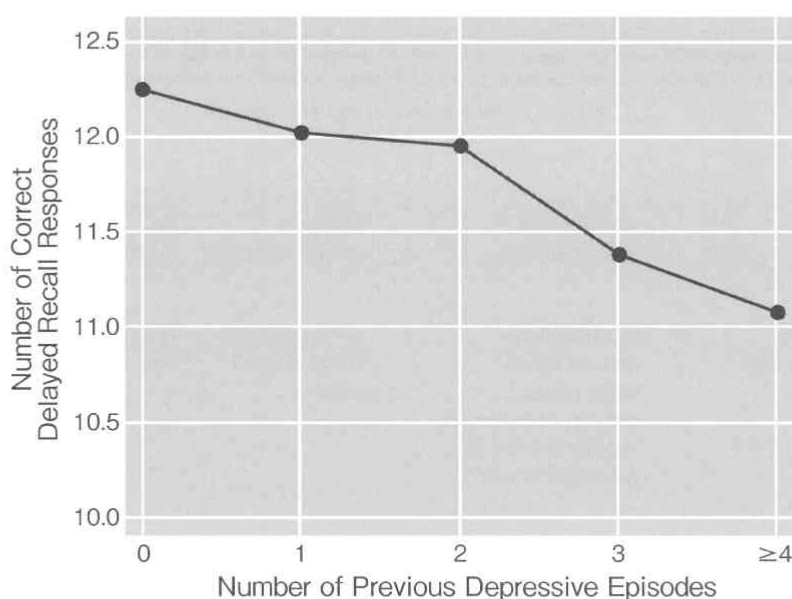


Fig. 9 Number of correct delayed recall responses at the second visit according to the number of previous depressive episodes in patients with major depressive disorder
(Gorwood P, Corruble E, Falissard B, Goodwin GM. Am J Psychiatry. 2008)

show dysfunction in all items studied including memory, psychomotor speed, response time, attention, and cognitive flexibility, with most significant dysfunction in attention. About 30.2% patients with bipolar disorder, 20.7% of major depression, and 19.0% of schizophrenia patients show below 2 SDs or more dysfunction in multiple items studied (Fig.8). Patients with major depression often show repeated episodes of depression, and it is known that delayed recall is impaired by repeated depressive episode (Fig. 9).

Introduction of DSM-5

American Psychiatric Association published DSM-5 in May 2013, which is the revision of previous DSM-III (1980), DSM-III-R (1987), DSM-

IV (1994), and DSM-IV-TR (2000). DSM-5 is a major revision after 19 years since the publication of DSM-IV. In the revising process of DSM-5, there had been a fierce dispute between the supporters of categorical model and dimensional model. The proponents for the dimensional model insisted on the diversion from long-standing traditional dichotomy of schizophrenia and mood disorders since Kraepelin's time by incorporating recent findings from biological psychiatry. The debate of "deconstructing psychosis" itself is interesting and published in the literature. Many psychiatrists were involved in the discussion and there was much expectation that DSM-5 would eventually incorporate the outcome from the discussions on dimensional model. The announcement of DSM-5 has attracted a great deal

of expectation.

After studying the published DSM-5, features of DSM-5 are summarized: (1) Transformation from categorical model to dimensional model approach was incompletely adapted, (2) Major items were sorted according to the life development model, (3) Major items were arranged considering the internalizing and externalizing factors, (4) The multi-axial diagnostic system was abolished, (5) Many specifiers are available, (6) For the evaluation of general function of patients, WHO Disability Assessment Schedule (WHODAS) according to ICF is adapted and GAF scale has been abandoned.

Due to high pre-publication anticipation, many opinions have been issued and published since the publication of DSM-5. Typical comments from Europe are cited here by Hans-Jürgen Möller and his coworkers: (1) The original plan to introduce dimensional model was not completed and DSM-5 was ended with the categorical model after all. (2) Biological findings such as biological markers, genetics, and brain imaging, were not sufficiently incorporated, and DSM-5 remained after all in the symptomatology-based descriptive classification. (3) The intention of introducing the dimensional approach was implemented by newly introduced "specifiers." (4) DSM-5 is still unclear whether these specifiers are fully utilized in clinical settings (Möller et al. 2014).

Difficulty in classification system of psychiatric disorder

Systemic classification of psychiatric disorder was first implemented by Emil Kräpelin in 1920 when he demarcated schizophrenia from manic depressive disorder. The difficulty in accurately classifying psychiatric disorders was pointed out by Kräpelin himself from the beginning. Kräpelin stated in his book; "The method applied so far to define morbid forms, taking into account the course, manifestations, evolution and the final stage, and postmortem findings, is exhausted and is no longer satisfactory. New ways must be sought out" (Kräpelin, 1920).

When DSM-IV-TR was announced, Steve-Hyman, then US National Institute of Mental Health (NIMH) director stated; "Approaches to diagnostic validity based on clinical description, laboratory studies, natural history of illness, and familial aggregation have not converted to yield a nosology based on valid disease entities. Defining a rational nosology for disorders of the brain is clearly one of the great challenges for modern

medical science (Hyman, 2002)."

After the publication of DSM-5 in 2013, Juan and Maria Lopes-Ibor stated "The great hope that DSM-5 could bring fundamental advances in our understanding of the genetic and environmental determinants of disease risk, and of the neural circuitry supporting normal and pathological mental processes has not been materialized in spite of extensive and intensive research efforts" (Lopes-Ibor et al. 2013a, 2013b).

Transition of classification systems and positioning of DSM-5

When we look back the history, psychiatry has clearly been developed by repeated swings between biological psychiatry and psychological psychiatry like a pendulum. The period of early 20th century when Emil Kräpelin proposed the two distinct entities of diseases, schizophrenia and manic depressive disorder, was the time of new biology where neuropathology was brought in as the new research technique. In other words, it was the days of high expectation for psychiatry to be developed along with biological science. In those days, Karl Jaspers stated, "In order to understand the psychiatric disorder, not only the description of the causal relationship with brain science, there is a need for understanding of the meaning contained in the psychiatric symptoms. Mental disorders demand meaningful understanding as well as the causal explanation delivered by the brain science. Translation of the objective findings of the brain sciences to meaningful life-world of every subjective experience is essential." (Jaspers, 1913).

In those days, the traditional psychiatry in Germany had accumulated many findings obtained through primarily neuropathological techniques. The swing of psychiatry pendulum was swayed predominantly into the direction of biological psychiatry, and the new trend in psychological psychiatry was still in premature stage until 1945. Just before and during World War II, many psychiatrists who moved from Germany to the United States, promoted the rise of psychological psychiatry in the United States. Consequently, psychiatry in the 1960s was biased towards to psychological psychiatry, and the pendulum of psychiatry was swung too much to psychological psychiatry. It was in 1959 that WHO summoned the meeting on classification system of psychiatric disorders, where the reliability of the diagnostic system was seriously debated. Experts in classification of psychiatric disorders were asked

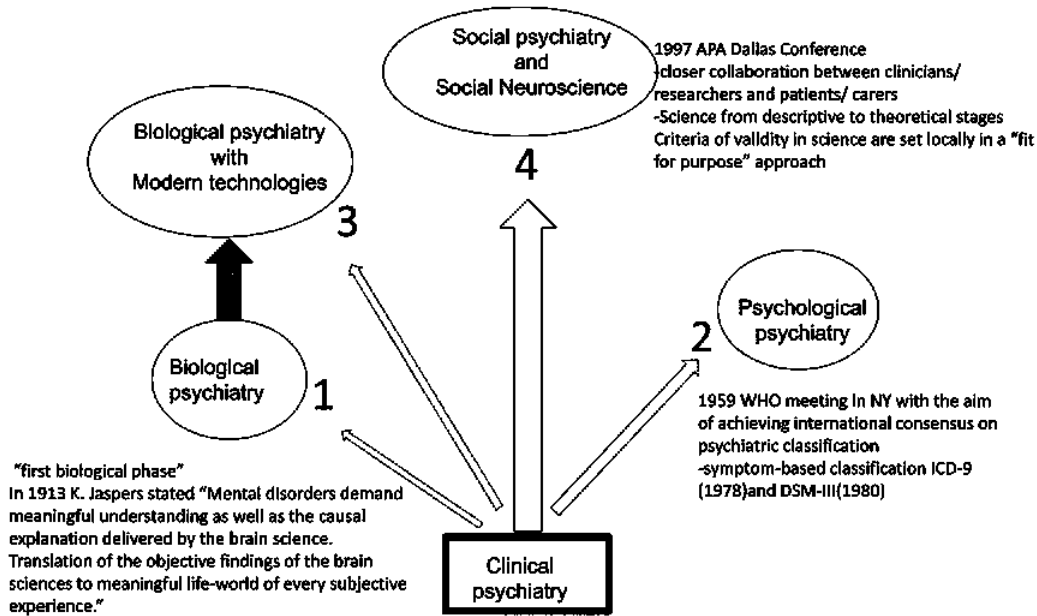


Fig. 10 Development of diagnostic classification system in psychiatry

for the means to increase the reliability of psychiatric diagnosis. As the important outcome from this meeting, a new classification system was proposed which could be used internationally with good reliability, and highly manipulative diagnostic system was developed as ICD-9 (1978) and DSM-III (1980), which was based on behaviors and symptoms observed from outside, trying to avoid any hypotheses or assumptions about the pathogenesis of psychiatric disorders. By effort of trying to attain objective diagnosis, psychiatry has returned to its pendulum again towards biological psychiatry, diverting from dependence on too much of psychology.

The next important step in revising classification system of psychiatric disorders was at the Dallas annual meeting of American Psychiatric Association (APA) in 1997. At this meeting, the corresponding measures to correct the negative effects of the DSM was put on the table, because serious negative feedback of DSM-III was the topics of the meeting. DSM-III was developed primarily to enhance the reliability of the diagnosis. The discussions were on the strategies how to enhance the validity of the diagnosis without losing the reliability of the diagnosis. Then the need for collaboration among clinicians, researchers, as well as patients and their families was proposed. This was the epoch-making, breaking away from the swinging motion of the pendulum between biological psychiatry and psychological psychiatry in the past. This was the first time for psychiatry that a new

stance with an eye to social psychiatry was put to the front. In order to add diagnostic system more usefulness, the reliability should be sought for "fitting for purpose" manner with collaborative work of patients, clinicians and researchers. The importance of the collaborative work was pointed out to evolve from descriptive diagnostic system to the theoretical diagnostic system. The importance of collaboration with patients and their family have been proposed (Fig. 10).

What is lost in DSM-5

Given the complexity of psychiatric disorders, DSM-5 itself does not mean a completed final version, but is probably continued to be revised into future revisions until it reaches the full-classification system. Further accumulation of knowledge and time will be needed for it. At the same time, the appropriate classification system is extremely important for the proper development of psychiatry itself, and the developed psychiatry will make further developed classification system feasible, vice versa.

Here, we point out some of the negative aspects that DSM-5 has brought in to research in psychiatry and neuroscience. As stated earlier, the primary goal of DSM-5 is to increase the matching rate of the diagnosis, i.e., higher reliability, which is attained by relying on observable symptomatology and statistical evidence. For the sake of high reliability, DSM-5 is reluctant to incorporate new findings especially

something based on theoretical thinking and biological findings. One drawback of DSM-5 is the lack of working hypothesis about the pathogenesis of psychiatric disorders. In other words, the validity of the diagnosis is not always secured under DSM-5 classification system, which can be misleading to biological studies of psychiatric disorders.

The diagnosis under DSM-5 is not intended to promote an understanding of the pathophysiology of psychiatric disorders. Rather, the imperative procedure when the diagnosis is made is to increase the number of matched items described under a certain category of psychiatric disorder. This procedure can be sometimes misleading to understanding of the disease. For example, major depressive disorder is diagnosed with more than five out of the nine diagnostic items matched, but there is always a question whether major depressive disorder is really the same disease that meets different set of items in DSM-5 criteria. Another obstacle in DSM-5 is that there are too many comorbid disorders diagnosed to a single patient in actual clinical settings. It is important to notice that DSM-5 does not include the findings of biological psychiatry such as brain imaging, brain physiology, molecular genetics, and others. It is also important to know that DSM-5 is an operative diagnostic system simply relying on the set of symptoms or combination of syndrome, nothing to do with disease entity, which might mislead the direction of drug discovery research of psychiatric disorder if it is not properly delineated.

Advocate of Research Domain Criteria (RDoC)

Remarks by Thomas Insel, the current NIMH director, to DSM-5 had a significant impact in academia. He is the person representing biological psychiatry, and his opinion can be taken as the departure from DSM-5. Insel stated; "the diagnostic system has to be based on the emerging research data, not on the current symptom-based categories. For what we need to do in mental health research — for what it is becoming clear we *can* do — the DSM approach is not appropriate. Even if it is still the best way to diagnose disorders and deliver treatment and knit the mental health care system together, it must begin to be supplanted by a new science-based framework" (Insel, 2013).

NIMH has launched the Research Domain Criteria (RDoC) project to transform diagnosis by incorporating genetics, imaging, cognitive science,

and other levels of information to lay the foundation for a new classification system. Through a series of workshops over the past 18 months, Insel has tried to define several major categories for a new nosology. This approach began with several assumptions:

- A diagnostic approach based on the biology as well as the symptoms must not be constrained by the current DSM categories,
- Mental disorders are biological disorders involving brain circuits that implicate specific domains of cognition, emotion, or behavior,
- Each level of analysis needs to be understood across a dimension of function,
- Mapping the cognitive circuit, and genetic aspects of mental disorders will yield new and better targets for treatment.

Thomas Insel and NIMH have launched the program for designing new diagnostic criteria of RDoC independent from for DSM-5 which is incorporating full utilization of recent knowledge in biological psychiatry. It aims for the elucidation of the five neural networks; negative valence systems, positive valence systems, arousal / modulatory systems, cognitive systems, and systems for social processes, which can be eventually used for creating diagnostic criteria of psychiatric disorders.

Brain connectome and network analysis

The Brain Activity Mapping Project in the United States and Human Brain Project of European Community were launched in 2013 with a huge budget investment. Even though these two projects are independently initiated, the goal of both projects are set to elucidate the brain specific function of human beings by analyzing all neural circuits in the brain by filling the gap between the intracellular electrode recording from a single neuron and the findings from brain functional imaging. It is expected to reveal the mechanism and function of neural circuit of the humans for the first time by analyzing the activity of every circuit consisting of numerous neurons. As the time schedule of Brain Mapping Project, it is expected to reveal the unique characteristics of neural circuit of the nematode (302 nerve cells), part of the brain circuit of *Drosophila* (15,000 nerve cells), the circuit of the mouse retina (about 50,000 nerve cells), and the circuit of mouse cerebral cortex slices (about 40,000 nerve cells) in five years. The whole brain of *Drosophila* (13.5 million neurons), the central nervous system of fish (1 million neurons), the entire cortex of the

Etruscan shrew (100 million units) will be attained in 10 years. Finally in 15 years, it is expected to decipher the circuit of the whole brain activity of mouse cerebral cortex to clarify the meaning of overall brain activity.

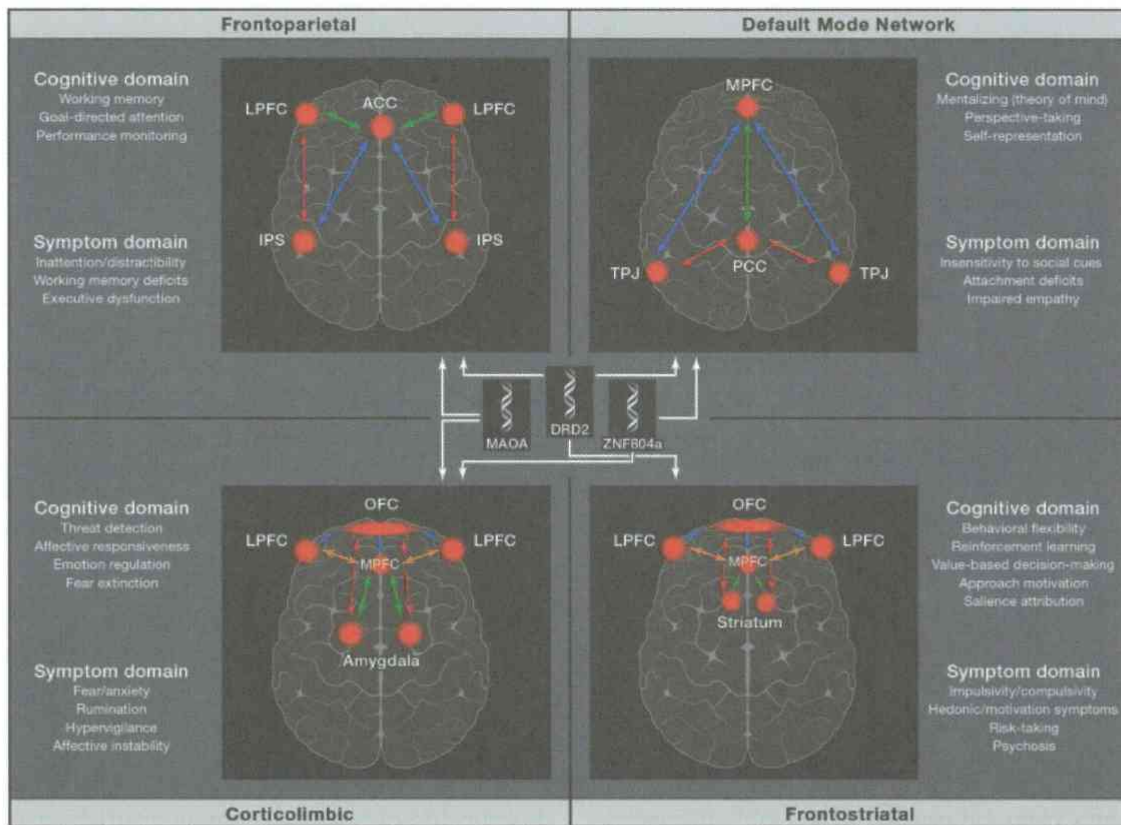
The present study of brain activity in humans has already shown that several sites are functioning cooperatively in the brain. Typical examples of brain circuit include: (1) the frontoparietal system involved in attention and cognitive control, (2) the cortical limbic system involved in emotional arousal and regulation, (3) the frontal striatal system involved in reward and motivation, and (4) the default-mode network (DMN) which is active during the state where nothing is seemingly executed but is believed to be involved in self-expression and social cognition (Fig. 11).

Each neural circuit is related with some type of psychiatric disorders, and further related with the

function of several genes. For example, the neural circuit representing the cognitive domain is involved with working memory, goal-directing attention, and performance monitoring, which will cause inattention/ distractibility, working memory deficits, executive dysfunction when this neural circuit is impaired by disorders. Since the related genes are partly revealed in these disorders, neural circuit analysis could be the link between genetic information and the symptoms caused by the disorder (Fig. 12).

How to secure the validity in diagnosis of psychiatric disorders

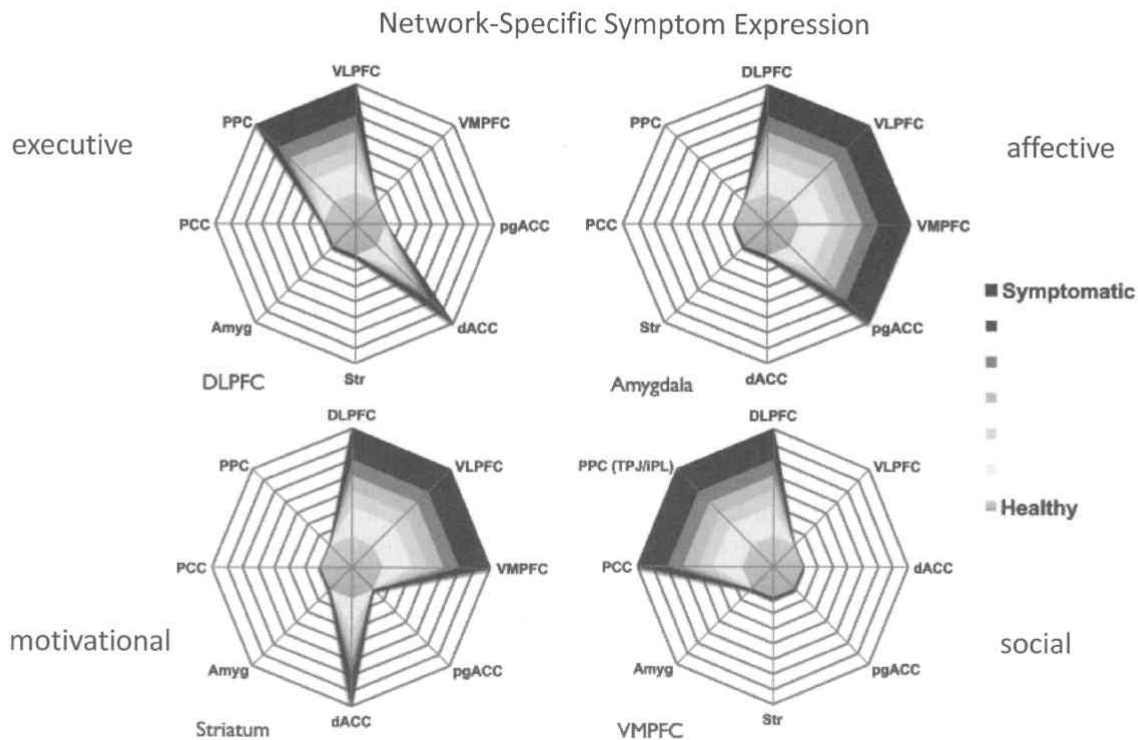
The goal of DSM-5 was, in simple words, to increase the matching rate of the diagnosis. The reliability of the diagnosis was set high priority, but the consideration of its validity remained insufficient. So, we should be equipped with the



Frontoparietal (LPFC-dACC-IPS), corticolimbic (LPFC-vmPFC/OFC/pgACC-amygdala), frontostriatal (LPFC-vmPFC/OFC-striatum), and DMN (VMPFC-PCC-TPJ/iPL) circuits underpin core executive, affective, motivational, and social domains of cognition, respectively. Heritable variation in the function of these circuits produces deficits in circuit-specific cognitive domains, which manifest as clinical symptoms. Circuit-specific, but transdiagnostic, cognitive processes (cognitive domains) and symptoms (symptom domains) are shown for each network. Allelic variants in MAOA, DRD2, and ZNF804A are shown affecting specific networks that may account for their observed pleiotropic effects, as indicated by available data.

Joshua W. Buckholtz, Andreas Meyer-Lindenberg: Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness, *Neuron*, Volume 74, Issue 6, 2012, 990-1004

Fig. 11 Example of brain networks representing attention and cognitive control, emotional arousal and regulation, reward and motivation, and default-mode network (DMN)



Idealized radar plots depict connectivity within four core networks for executive, affective, motivational, and social cognition, centered on DLPFC, amygdala, striatum, and VMPFC, respectively. Distance of each spoke from the center represents the magnitude of deviation in node-wise connectivity from "normal." Functional connectivity is considered here as a normally distributed quantitative trait; thus, "normal" can be thought of as the population mean. Units are arbitrary. Continuous variation in the function of these circuits leads to variability in expression of symptoms linked to each network, ranging from "healthy" (unlikely to cause psychological dysfunction) to "symptomatic" (associated with significant dysfunction, impairment, or distress). (Joshua W. Buckholz, Andreas Meyer-Lindenberg: Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness *Neuron*, Volume 74, Issue 6, 2012, 990-1004)

Fig. 12 Variability in circuit-level connectivity leads to variability in network-specific symptom expression

means to secure the validity of our diagnosis when we use DSM-5 in actual clinical settings.

Looking back the history, diagnostic system based on the German traditional psychiatry was the process of choosing the diagnosis by close observation of the abnormal behavior of the patient, by extracting the elements relevant to the diagnosis, and compare the validity of the diagnosis, which is quite different by experience and knowledge of the psychiatrist. Psychiatrists were loaded with huge task of picking the right diagnosis that seems to best suit from his experience and thinking. Therefore, there was a drawback that diagnosis does not always match by the discretion of experience. To exclude the drawback of traditional diagnostic system, DSM excluded the reasoning about the pathological process of the patients as the subjective judgement of a psychiatrist. The operational process of diagnosis in DSM intentionally avoided the psychopathological thinking, it simply relies on the process of combining a plurality of behavioral abnormalities observed from outside,

so that the number of matching items in the criteria is maximized. This kind of operational pragmatism can be applied in the process of giving diagnosis relying on behavioral characteristics and epidemiological evidence, without paying attention to psychopathological observation in the etiology and pathogenesis of psychiatric disorder. Several shortcomings of the operational diagnostic criteria have been discussed for many years since DSM-III in 1990s.

The attitude of "high reliability, less validity" as seen throughout the DSMs certainly has contributed to the improvement of the concordance rate of the diagnosis, but it pays less interest to psychopathological considerations of the patients. The important fact is that even if the higher matching rate of diagnosis is attained by DSM-5, we should be always cautious about the validity of the diagnosis.

What is validity of the diagnosis of psychiatric disorders? In science it is not always easy to secure the validity. The validity of the diagnosis in psychiatry should be considered from the

viewpoint of individuality, fitting in place, and suiting its purpose. Especially for the validity of the psychiatric diagnosis, many factors should be included; incidence, prevalence, predilection age, symptoms, signs, course, treatment response, and many others, which should be judged by a comprehensive manner.

Validity of psychiatric diagnosis should be sought in accordance with the purpose ("fit for purpose"), in consideration of the implications to the patient life, and the subjective experience of the patient. We would like to discuss the important points when considering the validity of psychiatric diagnosis.

1. What is meant by psychiatric disorder

Unlike other physical diseases, psychiatric disorder is a disease of "living humans." Psychiatric disorder is, in a sense, a disease of the brain and mind. But at the same time, the patients with psychiatric disorder live their life together with the disease. Most of physical diseases are the disease of a specific organ, in which the functional defect of the organ can be restored by intervention, and the patient can recover their full activity when it is restored. But it is not the case with psychiatric disorders. A patient with psychiatric disorder is a patient as a whole. Psychiatric disorder cannot be distracted from the patient life and patient himself. As an extreme example, T. Szasz who advocated an anti-psychiatry movement in 70s, said that psychiatric patients were all those produced by society segregation and he argued that there is no psychiatric disorder. Of course his idea is no more accepted, but there could be the room for discussion of what the psychiatric disorders is, especially in the borderline zone of psychiatric disorder and/or personality disorder.

The meaning of psychiatric disorder is quite different even to psychiatrists by the field of biological, psychological or social psychiatry. Disease model is easily accepted by biological psychiatrists, but psychological model is easier to be accepted by psychological psychiatrists. Considering the difference in understanding of psychiatric disorder, we have to bear in mind the possibility that no psychiatric disorder has solid evidence that it can be the real disorder or disease in the similar sense of physical disease in which the disease can be detached from the existence of the humans. Psychiatric disorder is a complexity of disease, disorder, dysfunction, and handicaps of the person living in the society.

2. "Understanding" of complex psychiatric symptoms

Psychiatric symptoms are expressed as abnormal behaviors in patient life as a multi-layered structure. Given the complexity of the psychiatric symptoms, it should be considered from both the observation of the patient's behavior and also from the expression of subjective experience by the patient. Unfortunately the remarks of the patient with psychiatric disorder have been unfairly evaluated. Because remarks by the patient with psychiatric disorder are sometimes difficult to be understood, often change depending on the situations, sometimes lack logical structure, the claims from the patients have been often ignored. Those subjective remarks and experience of the patient were not properly evaluated as those versatile objective evaluation.

Psychiatrists or clinical researchers are expected to acquire information from the patient and their family members. It is essential to collaborate with the patient for the successful translation of clinical experience to research. At least, it is essential from the side of clinicians and researchers to learn the subjective experience of the patient. Such efforts to acquire the information about individual differences of patients living in the society, and the meaning of symptoms to patient life and their family is necessary. In this sense, clinicians and researchers as expertise-by-training is expected to collaborate with the patient and family as the expertise-by-experience.

3. Reconsider the meaning of psychiatric symptom

For many chronic diseases, there are two different models of recovery; medical model and recovery model. Medical model means symptom suppression because medical treatment is mainly aimed for the suppression of the symptom. The other is recovery model in which more attention is paid to quality of life (QoL) rather than the symptom suppression. The divergence between the above two models are often observed with chronic diseases. Dissociation between medical and recovery model is often seen in psychiatric disorders, and the symptom suppression and QoL do not necessarily correlated each other in psychiatric disorders.

Here we would like to raise the question whether all psychiatric symptoms are worthless. Some novelists or artists in hypomanic state create high-quality works. Autism patients might have difficulty in interpersonal relationship in their

working place, but they are good in giving calm judgment without being bound to human relations. In some information technology companies, an individual with autistic tendency is evaluated highly for their efficiency in the work requiring fine attention such as productive line of printed base of electronics. Schizophrenic patients can be engaged silently in a simple and tedious work. Given such examples, we cannot say that all of psychiatric symptoms is worthless. Some of psychiatric symptoms need to be reconsidered in terms of extending the advantage due to psychiatric symptoms and those to be controlled. Meaning and value of psychiatric symptoms are necessary to be reconsidered when we think about the patient's QoL and well-being.

History of intervention and treatment of psychiatric disorders

Until the early 19th century when Filipe Pinel released the chain of the patients with psychiatric disorders, disabled persons with psychiatric disorders were not recognized even as human beings. With the statement of Binswanger that "psychiatric disorder is a disease of the brain," patients with psychiatric disorders were for the first time recognized as the person dysfunctioned by brain disease. However, during the first half of the 20th century, there had been nothing as the effective treatment of psychiatric disorders. It was only in the second half of the last century when the development of anti-psychotic drugs was initiated in 1950s so that the first effective therapeutic intervention was applied to psychiatric disorders.

Representative of the first generation of anti-psychotic drugs was chlorpromazine discovered by Delay and Deniker, pioneers in psychopharmacology. It was understood that anti-hallucination/ delusion action is observed for the dopamine D₂ receptor antagonists, and it became possible to reduce the pathological experience of many patients with schizophrenia. However, drug-induced Parkinsonism as an adverse side effects of the D₂ blockers was at the same time popular, and side effects of extrapyramidal symptoms were forced to the patients for therapeutic effect. The side effects of D₂ blockers were admitted inevitable for the sake of improvement in psychiatric symptoms for many years. When we stand in the position of the patients, auditory hallucinations and delusions were certainly reduced with pharmacotherapy, but there was also inconvenience of extrapyramidal symp-

toms at the same time which was brought about by the drug usage. Many of the psychiatrists considered such inconvenience of patients to be endured for the sake of control of pathological experience.

It was only after the introduction of the second-generation anti-psychotic drugs that unwanted-extrapyramidal symptoms were believed to be avoided, it was the initial phase of pharmacotherapy to listen to subjective experience of the patient. Then, in the second-generation of anti-psychotic drugs, a few agents having an effect to the negative symptoms even incomplete were developed in addition to the effect to the positive symptoms. It has made it possible to listen to the voices of the patients on their experience, who have been significantly suppressed to raise the voice due to lack of spontaneous subjectivity. Considering the history of development of pharmacotherapy over half a century from the introduction of the first drug, we have finally reached the stage where we psychiatrists can try to hear the experience of the patient as his own voice.

A similar situation is also true for the development of antidepressants. Imipramine was surreptitiously developed in the 1950s as the first tricyclic antidepressant. Many tricyclic antidepressants were developed following imipramine, all of which had adverse side effects mainly due to its anticholinergic effects. The tetracyclic antidepressants were then developed for the relief of adverse side effects. Now we are using many kinds of serotonin selective re-uptake inhibitors (SSRIs) as the first choice to treat the depressive patients. Antidepressant effect of SSRIs might be substantially the same as that of tricyclic antidepressants but adverse side effect of SSRI has been significantly reduced. The introduction of the antidepressants with reduced side effects, has led to major changes in drug therapy for depression. It was not possible for the depressed patients to raise the voice for the symptoms, but now for the first time the subjective experience of the depressed patients can be heard by the use of suitable antidepressants.

Collaboration between clinicians, researchers, patients and their families

Collaboration of clinicians and researchers with patients and family members will be required for the future development of psychiatry. When we recall the words of Jaspers in 1913, "to psychiatric disorder, it is necessary to understand the meaning of the disease as well as description of

the causal relationship that is brought about by the knowledge of brain science, " (Jaspers, 1913)

The author's proposal may not be new because the message is more or less similar with that of K. Jaspers, but I would like to point out that we are finally in the time where we can hear the voice of the patient owing to the advance in pharmacotherapy. Our clinical situation allows us to listen to the patient's voice to understand the patients experience into research. The future of psychiatry depends how properly we will evaluate the subjective experience of the patient. It would be important to wear the ability to perceive and to understand the meaning of psychiatric symptoms.

How we should evaluate psychiatric symptoms

In the long history of psychiatric service in the past, psychiatrists had struggled for the objective evaluation of the patients, and in return, psychiatrists have truncated too much the subjective experience of patients. Now it is the time for psychiatrists and researchers to collaborate with patients and families. It might be the only way for future psychiatry to promote collaboration to evaluate properly the experience of the patient.

Evaluation of psychiatric symptoms can be done in objective way and in subjective way. Many kinds of scales and measures exist to be used in clinical settings of psychiatry. Any measures or scales can be used for different purposes in different clinical settings. Regardless of measures and scales, understanding of the patient as a whole is the most important to evaluate the effect of the psychiatric therapeutic interventions, and the following points should be born in mind.

1. Whose outcome?

The most important viewpoint is whose outcome should be evaluated when we need to evaluate the effect of the intervention. Psychiatric disorder is itself complex, and there might be instances where the effect of therapeutic intervention may be evaluated from the society's view point as a whole rather than for the patient. In the past in some countries, there used to be policies for psychiatric disorder which deviated significantly from the patients' point of view, rather it was discussed from the view point of caregivers, medical staff, or the community. However, in order for psychiatry to grow as useful service to the patients in the true sense, of

course, we should not forget the point of view of the patient.

2. Which area should be evaluated?

Psychiatric symptoms are complex enough in themselves. Patients may show symptoms of various areas such as behavioral abnormality, cognitive dysfunction emotional instability, making invocation, and others. When we evaluate the effect of intervention, we should be careful enough to choose which areas of symptoms should be evaluated. There can be measures for subjective satisfaction, stability of the patient's emotion, cognitive function, the patient's health, interpersonal relationship, and social services utilization.

3. In which level?

Psychiatric disorder may induce dysfunction at any levels in the hierarchy of biological, psychological, or social structure. In accordance with the respective methods of intervention, we should pay more attention to which level should be selected to evaluate the intervention effect at any level, such as individual level, interpersonal level, or society level in the whole. For the evaluation of individual level, we will pay more attention to the symptom changes, but when we are talking about interpersonal level, there might be the relationship with the carers, family members, or the thing in community networks can be evaluated. In addition, when we evaluate on the society level, prejudice, or stigma also can be considered as important measures for intervention.

4. Symptom suppression model versus recovery model

In many acute physical diseases, recovery from impaired function will usually be the same with the suppression of the symptoms, which is not necessarily the case in chronic diseases such as psychiatric disorders. For example, in a case of colon cancer, surgical treatment is recommended to save the life of the patients. Surgery can be the choice of treatment of cancer by excising cancer tissue, but the patient may face with inconvenience of reconstructed bladder and/ or artificial anus which may reduce the QoL of the patients. For psychotic patients, a large amount of psychotropic drugs may be prescribed in order to suppress hallucination or delusion, but there are cases where physical fatigue and sleepiness appear by a large dose of pharmacotherapy. Generally speaking, suppres-

sion of hallucination/delusion to a certain level with minimum dose of antipsychotics is better for the patient quality of life even though high dose of the drug is necessary to have the complete suppression of psychotic symptoms. This is not a simple choice between symptom suppression model or recovery model as an alternative choice. Rather we recommend to include the evaluation of subjective experience of the patient, such as HONOS, CORE-OM, OQ-45, and CAN.

5. Individual versus overall evaluation

Since psychiatric symptoms are complex, many rating scales are developed to evaluate the symptoms in distinct areas of mental function. But mental function of the patient is not the simple summation of individual score of each mental function. The eventual evaluation of the patients should be aimed to know how the patients are happy as a whole. The evaluation as a whole person is more meaningful as the evaluation of intervention rather than the individual area. Evaluation as the entire human beings should be used, such as goal attaining scale (GAS), Personal Primary Outcome (PPO) list, or INSPIRE score.

6. Disadvantage versus advantage

To evaluate overall function of the patients, there might be two different approaches, one is to evaluate the defect, and the other to evaluate advantage. When we are dealing with the patients showing some defect due to certain biological disease such as cerebral infarction in certain areas, it is easily understood by evaluating the defect caused by the disease. We can easily understand the direct causal relationship of the defect of the patients and the effect of intervention. In most of complex symptoms of psychiatric patients, however, we may be sometimes lead to wrong conclusions if we pay our attention only to unnecessarily deficiency alone. Evaluating the advantage of the patients may often lead the correct evaluation as overall proactive experience. Subjective Happiness Scale, WHO-5 Well-being Index, Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) can be used for the index which can give the information from the patients as the subjective experience as a whole.

7. Who's view point

Subjective experience of the patient will be more important for the future psychiatry than ever. Patient rated experience measures (PREM), patient rated outcome measures (PROM), patient-

generated PROM (PG-PROM) can be used more in clinical settings to emphasize the patient's viewpoint.

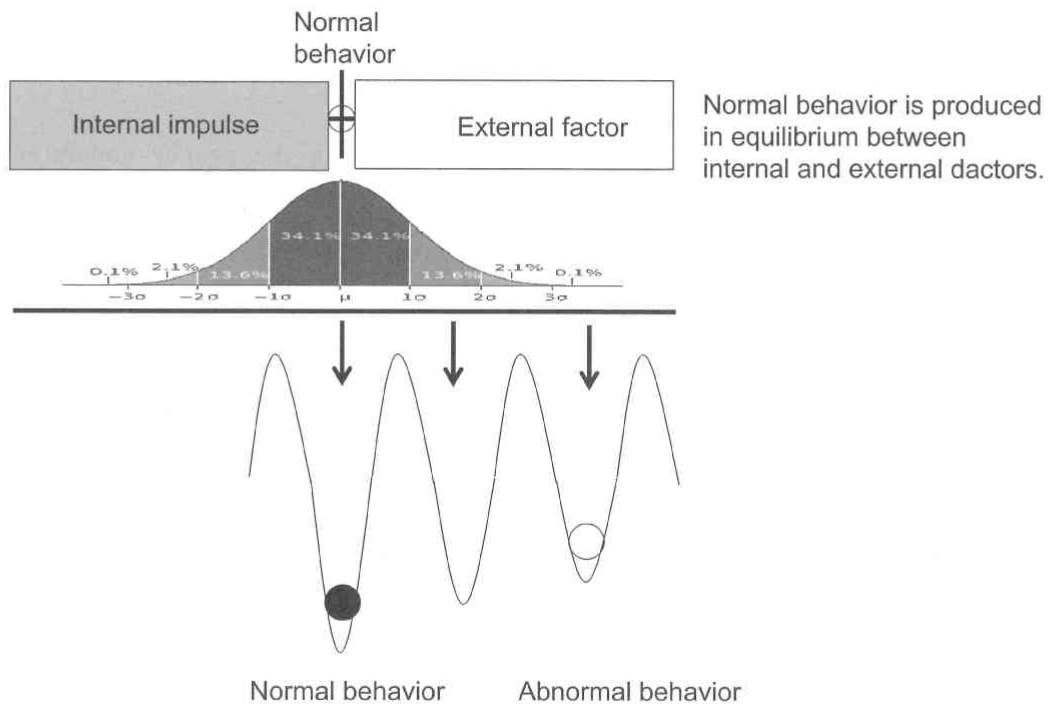
How to attain the proper understanding of psychiatric symptoms

Human behavior is defined by the equilibrium between the inner impulse and the cognition of outside stimuli. Although the behavior of most of the healthy people falls within a certain range, the behavior of psychiatric patients might deviate from the range of such a healthy person. When internal impulse is too strong, or perception of external stimulus is inappropriate, the behavior of the patient is deviated significantly from the average value (Fig. 13). When we consider human behavior together with the notion of neural circuitry of the brain, we can draw a schema as depicted previously in Fig. 12. Human behavior is defined by the network activity of each region, the activities of each of the network defined by the stable state of each domain. In the brain circuitry recognizing external stimuli, there might be several alternate stable states. Then, by psychiatric disorder, we think the network steady state is stable beyond the scope of normal person.

To correctly understand the meaning of the psychiatric symptoms, it would be necessary to expand the framework of the observers' common sense. For this purpose, it is required to enlarge the width of the activities for each of the brain network as shown in Fig. 14. Listening to the voice of the patient, and trying to understand the subjective experience of the patient is helpful to increase empathy with the patients, and it may help broaden the width of such brain network.

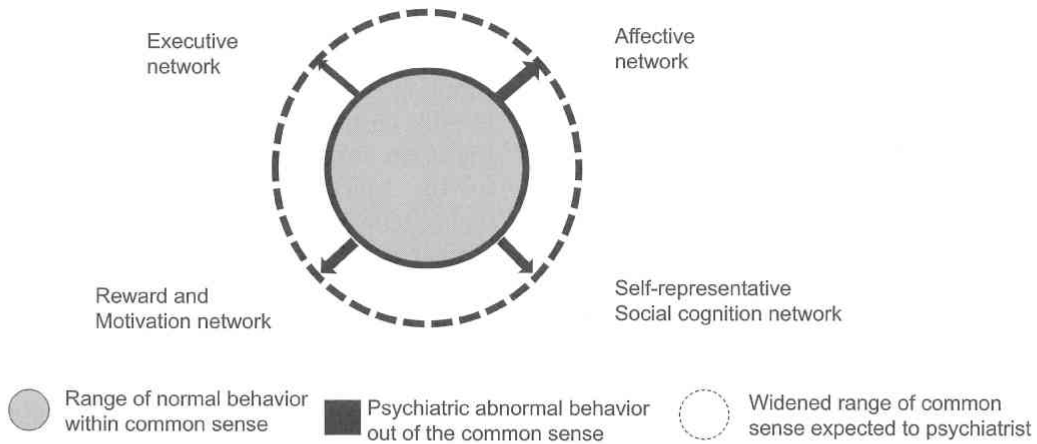
As said by Jaspers, it is important to understand the meaning of psychiatric symptoms. Trying to interpret the words by Jaspers in a modern sense, I would like to conclude the paper by the comments below.

It is important to perceive and understand the subjective experience of the patient, and the subjective experience of the patient should be properly evaluated by psychiatrists, which is the only way to implement the patient-centered service. In addition, psychiatrists, as professionals facing the patients with psychiatric disorder, are expected to increase their ability of understanding by broaden the framework of their common sense, so that they can perceive, sympathize, and understand the voice from the patients.



Human behavior is selected and produced as the equilibrium of internal impulse and external factors. The output behavior is ranged in certain range around the mean output as the normal behavior. In psychiatric patients, the output of behavior can be out of the common range, below or over 2 standard deviations, which is sometimes understood by the people. There are several steady states of the brain network which produces normal and abnormal behaviors.

Fig. 13 Output mechanism of human behavior



The common range of behavior is the product of several brain networks including executive, affective, reward and motivation, and self-representation. Each domain can be abnormal with psychiatric patients. To properly understand the meaning of these psychiatric symptoms, psychiatrists themselves are expected to expand the range of these networks.

Fig. 14

References

American Psychiatric Association The Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition (DSM-5), Arlington, Virginia, USA: American Psychiatric Association.2013

Buckholtz JW, Meyer-Lindenberg A: Psychopathology and the connectome: toward a transdiagnostic model of risk for mental illness. *Neuron*, 74: 990-1004, 2012

Gorwood P, Corruble E, Falissard B, Goodwin GM: Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am J Psychiatry*, 165: 731-9, 2008

Gualtieri CT, Morgan DW: The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry*, 69: 1122-30, 2008

Hyman SE: Neuroscience, genetics, and the future of psychiatric diagnosis. *Psychopathology* 35: 139-44, 2002

- Insel T, blog, at <http://www.nimh.nih.gov/about/director/index.shtml/> May 2013
- Jaspers K: Allgemeine psychopathologie: ein leitfaden für studierende, ärzte und psychologen. Springer. 1913
- Kraepelin E. Die Erscheinungsformen des Irresein. *Zschr Neurol* 62, 1, 1920
- López-Ibor JJ, López-Ibor MI Paving the way for new research strategies in mental disorders. first part: the recurring crisis of psychiatry. *Actas Esp Psiquiatr*, 41: 33-43, 2013a
- López-Ibor JJ, López-Ibor MI: Paving the way for new research strategies in mental disorders. second part: the light at the end of the tunnel. *Actas Esp Psiquiatr*, 41: 67-75, 2013b
- Möller HJ, Bandelow B, Bauer M, Hampel H, Herpertz SC, Soyka M, Barnikol UB, Lista S, Severus E, Maier W: DSM-5 reviewed from different angles: goal attainment, rationality, use of evidence, consequences-part 1: general aspects and paradigmatic discussion of depressive disorders. *Eur Arch Psychiatry Clin Neurosci*, 265: 5-18, 2015
- Roitman SE, Keefe RS, Harvey PD, Siever LJ, Mohs RC: Attentional and eye tracking deficits correlate with negative symptoms in schizophrenia. *Schizophr Res*, 26: 139-46, 1997
- Takeda M, Shen WW: The hypothesis of cognitive reserve. *Taiwanese Journal of Psychiatry (Taipei)* 2015; 29: 70-79, 2015