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To what Degree Has Biological Psychiatry Realized Kraepelin's Dream?: Rhetoric of Species and Types

Masanari ITOKAWA1,2, Yasue HORIUCHI1,2, Kazuya TORIUMI1, Akane YOSHIKAWA1, Hiroaki ISHIDA1,2, Kazuhiro SUZUKI1,2, Yasuhiro MIYANO1,2, Tomoko INOUE1,2, Akiko KOBORI1,2, Mitsuhiro MIYASHITA1,2, Ryuta MIZUTANI3, Makoto ARAI1,2

1 Schizophrenia Research Project, Tokyo Metropolitan Institute of Medical Science
2 Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital
3 Department of Applied Biochemistry, Tokai University
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Abstract

We hypothesized that schizophrenia includes several natural species in order to perform genetic studies and identify biomarkers in this huge disease type. Kraepelin was thought to consider the hypothesis of natural species because he expected the neuropathological alteration of schizophrenia when he created the concept of Dementia Praecox with progressive prognosis. We introduce natural, substantial and ideal species to discuss the reasons for the difficulty of genetic studies and drug development for schizophrenia from the point of view of the disease as a type. We detected small species from the large type and depict what schizophrenia is at the end of our manuscript. The rationale of the endogenous disease proposed by Jaspers and Schneider as a brain disorder was also considered.

Keywords：natural species, substantial species, type, convergent evolution, limit cycle

Introduction

Kraepelin introduced dementia praecox in the fourth edition of his textbook in 1893. About 20 years earlier, in 1874, Carlbaum proposed catatonia, and Hecker introduced hebephrenia in 1871. Kraepelin attempted to position psychiatry within the natural sciences by proposing a new concept of disease that incorporated the classical psychiatry written about 20 years earlier. The reason is that he aimed to establish a disease entity on the basis of the development of the condition and terminal stage. In the 5th edition, he divided disorders into congenital and acquired, and in the 6th edition, he listed dementia praecox, manic-depression, and paranoia 17). Many psychiatrists brought up on DSM may not know how schizophrenia came into being in this way. In the first place, our search for genes and biomarkers is based on the assumption of a natural species, but can we leave the contradiction that schizophrenia is an ideal type unresolved?

There are two types of psychiatric disorders: those that are clearly pathological, such as visual hallucinations caused by brain tumors, and those that are not pathological, such as gambling disorder (e.g., a person who earns enough money to make a living from gaming competitions and is envied by the world and proud of him/herself) 10). Psychiatry is a special field of medicine that deals with disorders deeply connected to social adaptation and social values, such as gaming disorder, as well as biologically defined disorders such as exogenous psychosis. Among them, schizophrenia is an endogenous disorder that falls between the two - a social disorder and biological disease. What does it mean to be between a gaming disorder and brain tumor?

Among natural species such as cats and aluminum, those whose "essence" can be specified are called substantial species. For example, copper is a substantial species that consists of the Cu atom with atomic number 29 as its essence. On the other hand, there are types of species that consist only of definitions, i.e., those that are neither natural nor substantial species, such as dictators and graduate students. Although Kraepelin classified mental disorders into two categories based on their longitudinal course, with the aim of creating natural species, the reality is that they are defined types, such as graduate students.

In 2011, Nature reported that megapharmaceutical companies around the world had withdrawn from the development of drugs to treat psychiatric disorders 1). One of the

reasons for this is that even if proof of concept (PoC) is established in a small sample, it is difficult to find a significant difference from a placebo when the number of subjects is expanded. This structure of a small sample being rejected by a large sample is very similar to the situation in genome research, which has been struggling for nearly 30 years. In other words, a gene polymorphism that shows a large odds ratio in a small first report will show only a small odds ratio when a large sample is accumulated in a meta-analysis.

In this paper, we would like to consider "what is schizophrenia?" while touching on syndromes (types) and diseases (species), matters and events, natural and entity species, etc.

This study was approved by the Research Ethics Committee of the Tokyo Metropolitan Institute of Medical Science and collaborating institutions, and was conducted with written explanation given to and consent from the subjects.

I. The matter and event

Why do drug development and genome research for schizophrenia face difficulties? To answer this question, we begin by reviewing the history of the formation of the concept of mental disorders.

Until the 19th century, the term "mental disorder" meant only a state or syndrome, i.e., a bundle of symptoms that were transversal (present at the time of the disorder) 15). Pinel (1745-1826), who freed the sick from their chains at the Salpêtrière Hospital, stated: "It is a false choice to study the insanity as a separate thing, (omitted) and only by studying the characteristic qualities that appear as external signs (omitted) can we avoid going astray." He believed that mental disorders were not matters (substances) but events (condition) 16).

Kraepelin (1856-1926) emphasized the longitudinal (past, present, and future) outcome rather than a cross-sectional bundle of symptoms. In other words, he attempted to view mental disorders as disease entities (matters or substances) by contrasting the poor prognosis of dementia praecox with the good prognosis of manic-depressive illness. It is as if he were aiming for the substantial species (espéce naturelle) of Linnaeus (1707-1778), the 18th century Swedish naturalist who classified organisms into an elaborate hierarchical structure.

It is important to note here that Kraepelin placed the future in the scientific analyticity of neuroanatomy. He stated that he hoped that the development of natural science would eventually establish neuropathological findings and elucidate the causes of

schizophrenia 20). Kraepelin's two major classifications were subsequently passed on to Bleuler (1857-1939) and Schneider (1887-1967), who formed the so-called Kraepelin School, which became the mainstream of German psychiatry. Those were passed on to the Anglo-American community with marked simplification, and became the basis of ICD-10 and DSM-5.

On the other hand, the theories of Wernicke (1848-1905), who took the opposite position to Kraepelin's dichotomy, were succeeded by Christ (1879-1960) and Leonhardt (1904-1988), and became the Wernicke school 6). Wernicke aimed to conceptualize syndromes corresponding to the brain localization, or he took the position of association cortex connectivity disorder (network disorder)12), and the current brain morphological imaging or functional brain imaging research may be connected to this. Leonhardt placed nonsystemic schizophrenia, which shows good drug responsiveness and large genetic factors, in contrast to systematic schizophrenia, which shows poor drug responsiveness and small genetic factors. Leonhardt's schizophrenia is a disease entity (matter/substance) that takes heredity into account, and our specialty, genomic research, may be related to this lineage.

Thus, schizophrenia was created through the hands of many psychiatrists. As can be seen from the history of the birth of this disease, it is decisively different from the discovery of the neutrino or *Mycobacterium tuberculosis*. This is because the latter means that the invention of detection systems and advances in detection accuracy made visible what had existed before, while the former merely gave a name to what became visible by switching longitudinally from a cross-sectional field of view. Therefore, unlike neutrinos, there was no entity that existed before Kraepelin, and on the contrary, if one strives to look at the post-Kraepelin present in a cross-sectional manner, a pre-Kraepelin image immediately emerges. Diagnosis of mental illness is thus a process of superimposing the findings of the case before one's eyes on a template of typology.

II. Saddam Hussein and aluminum

Saddam Hussein and Hitler are called dictators because they fit the template of "rulers who exclusively exercise absolute power". Zebras and aluminum, on the other hand, are natural species defined by their genomes and elements. Although Kraepelin separated schizophrenia from manic-depressive illness by the category of "progressive and poor prognosis," it is considered that he was aiming for a natural species because he expected neuropathological

alteration (matter).

Linnaeus, who organized natural species and was also called the father of taxonomy, classified plants and animals into kingdom, phylum, class, order, family, genus, and species, but it is important to note that he selected the similarity of the morphologies subjectively. For example, one of the conditions for natural species of plants and animals is the ability to interbreed, because if the number of chromosomes and genome structure differ, they cannot be considered the same species because fertilization is not possible in the first place. However, the similarity of genomes does not always correspond to the morphological types subjectively determined by Linnaeus. For example, the sugar glider (*Petaurus breviceps*) is a marsupial, but it morphologically resembles the flying squirrel (*Pteromys momonga*) (Fig. 1). This is known as convergent evolution, in which species separated from each other in phylogeny become similar in appearance on living in a similar environment. Since Kraepelin's two major classifications are also typological, there is no guarantee that they reflect essence - a specific state of the brain that is causally coupled to symptoms - as in convergent evolution.

III. Natural and substantial species

Doctor Alzheimer, whose name is now synonymous with dementia, was initially challenged by the neuropathology of schizophrenia. However, he then continued to narrow his research to only those diseases with a set of "neuropathology-symptoms-progress-outcomes" that could be expected to be natural species. This is why neurological diseases such as Huntington's chorea and dementia could become natural species. In other words, Kraepelin classified the remaining diseases that failed to become natural species into two major groups: diseases with a poor prognosis and those with a good prognosis.

As mentioned above, natural species include substantial species whose essence can be specified. Copper, for example, is a typical example of a substantial species composed of Cu (essence) with atomic number 29. On the other hand, a "dictator," for example, is not a substantial species. Therefore, no matter how much we scientifically scan the body of a dictator, we cannot discover the essence (e.g., the dictator's genes) that causally determines the dictator. In that regard, diabetes and hypertension have taken on a somewhat substantive nature. This is because we can specify the plasma glucose level (mg/dL) and pressure of blood vessels (mmHg) as essential entities. However, the gerrymandered* influence what values must be exceeded in order to

qualify as a disease.

Science is precisely the activity that aims to specify the nature of a disease. However, because schizophrenia is neither a natural nor substantial species, not only neuropathology, but also genomic research and the development of antipsychotic drugs continue to face difficulties. Increasing diagnostic accuracy does not transform a typology into a substantial species. This is evidenced by the fact that the diagnostic categories of patients have continued to change gerrymandered with each revision of DSM.

In the case of physical diseases, the species (disease) has been established by studying the typologies (syndromes). For example, acquired immunodeficiency syndrome was a type (syndrome) characterized by reduced immunity, Kaposi's sarcoma, malignant lymphoma, and young men, but the species (disease) called HIV infection was established when human immunodeficiency virus (HIV) was discovered in patients at the Pasteur Institute. Why is it that a species can be established from a type in the case of physical diseases, but not in the case of mental diseases? It derives from the fatal difference between the metaphysical ideal type of the disease concept and somatic essence being real at the physical level. For example, in the case of ureteral stones, the onset of the disease is a stone lodged in the ureter, and the cure is when the stone is expelled during urination. In other words, the disease is defined in terms of a clear state of substances (physical), i.e., stone lodgment and stone fallout. Therefore, if we search for the physical essence from the type (syndrome), we can identify the entity and form of a species (disease). On the other hand, mental disorders such as eating disorders and schizophrenia are metaphysical types involving matters (brains) and occurrences (events). Therefore, it is not easy to find the essence of the physical from a group of metaphysical concepts.

IV. To solve metaphysical typology

We considered that the essence of schizophrenia could never be specified if we remained with the typology of dictators such as Saddam Hussein, so we abandoned the idea of finding a species (disease) from a syndromic population and instead devised a strategy to biologically enclose a typology (syndrome). Specifically, we focused on the progressive course of Kraepelin, and by analyzing only severe schizophrenia, we aimed to specify the essence that determines this progressive course. In other words, we sought to discover the substantial species that are the essence of the determinants of progression.

As a result, we identified a case in which the gene for glyoxalase 1 (GLO1), an enzyme that inhibits Advanced Glycation Endproducts (AGEs), was reduced in activity by 50% due to a frameshift mutation in a family with multiple cases of schizophrenia, and identified a metabolic disorder (carbonyl stress) that causes accumulation of AGEs in this case. In peripheral blood, AGE levels were 3.7 times higher than in healthy subjects, and vitamin B6, which inhibits the formation of AGEs, was reduced to less than 20% of that in healthy subjects.

We measured AGEs and vitamin B6 in 45 schizophrenic patients and 61 healthy controls to extract the substantial species that are essential for AGEs. It is as if to distinguish between the squirrel *Pteromys momonga* and marsupial sugar glider from a typological population with flying squirrel morphology. Subjects with diabetes mellitus and renal dysfunction, which are the major producers of AGEs, were excluded from the study. The results showed that AGEs were significantly elevated in 46.7% of schizophrenics and vitamin B6 was significantly decreased in 57.8% of schizophrenics 2) (Figure 2). If AGEs are the essence of the "progressive course," we hypothesized that if the essence (AGEs) could be eliminated, progression could be suppressed (symptoms improved). Therefore, we conducted a physician-led clinical trial to eliminate AGEs using pyridoxamine, an unapproved vitamin B6 with an inhibitory effect on AGE production. Ten schizophrenia patients with AGE accumulation in the absence of diabetes and renal dysfunction were treated with exploratory pyridoxamine at 1,200 to 2,400 mg/day for 6 months, and changes in severity were examined. The trial results showed that the mean reduction of plasma AGEs in the subjects reached 26.8%, and the severity assessed by the Positive and Negative Syndrome Scale (PANSS) improved by 10.8% on average, with a significant decrease in negative symptom scores in the two most effective cases 7). These results suggest an association between removal of AGEs and symptom improvement, as per the concept of the clinical trial.

V. Kraepelin's prophecy

As described above, these results suggest that schizophrenia associated with carbonyl stress may be a substantial species whose essence is the accumulation products (AGEs) of metabolic disorders. Interestingly, in the fifth edition of his 1896 textbook, Kraepelin classified dementia praecox as a metabolic disorder along with myxoedema. This suggests that he may have associated the poor prognosis with metabolic changes.

If we can extract the substantial species for which we designate AGEs as the essence from the huge typology laid down by Kraepelin, then we should be able to identify the neuropathological alteration he predicted in this population. We used nanotomography, a technique that analyzes three-dimensional structures imaged with electromagnetic radiation (synchrotron radiation) at the nanometer scale, to examine the neural structures of the anterior cingulate gyrus (BA24) of four schizophrenic patients, including one with carbonyl stress, and four control patients. Postmortem brains were Golgi stained to make neurons visible with X-rays and imaged at SPring-8, a large synchrotron radiation facility in Japan, and at the Advanced Photon Source at Argonne National Laboratory in the United States. Three-dimensional neural network images were traced by a machine recognition algorithm, and three-dimensional curves were represented by geometric parameters to analyze 2,592 neuronal outgrowths in schizophrenia and 2,068 neuronal outgrowths in controls. The results showed that the curvature of neurites in schizophrenia was 1.5 times greater than that in controls. The curvature of neurites was inversely proportional to their thickness, with the more curved neurites having thinner fibers. Action potentials transmitted to nerve fibers can be explained by a physical model of ion exchange within and between axons through the cell membrane (cable theory) 5). In this model, the transmission of action potentials is described by viewing nerve fibers as cables. According to this, the distance traveled between the two points where nerve fibers connect becomes longer because the greater the curvature, the more they meander, and the thinner the fibers, the more the action potential is attenuated. This suggests that schizophrenia may inhibit communication with neurons that are farther away than controls. Moreover, the highest curvature rate among the four schizophrenia cases was observed in a carbonyl stress case with a frameshift mutation in GLO1 13). Furthermore, when the superior temporal gyrus (BA22) was also examined, the curvature of neurite outgrowths differed between BA22 and BA24, both between individuals and between the disease and controls 14) (Figure 3). This suggests that the pathological process predicted by Kraepelin may differ among brain regions.

Kraepelin hoped that the development of natural science would establish neuropathological findings. At least some of his hopes may be fulfilled in the form of microscopic structural changes in the nerves.

Conclusion

What does it mean to be schizophrenic? What does it mean to be between a gaming disorder and brain tumor? A simple examination of the idea that schizophrenia can be a natural species will provide some insight into the legitimacy of current genetic research and the development of therapeutic drugs. This is because some areas of current neuroscience are amenable to exploration and development, while others are not at all 11). For example, in the area of instrumental brain functions such as vision, hearing, and memory, we have achieved a stage where we can freely describe and predict these functions, from animal models using optogenetics to human studies using functional brain imaging. On the other hand, can the fact that we are able to describe schizophrenia using research methods in these areas be said to be as impressive as vision and hearing? We have certainly accumulated a vast number of snapshots of the brain, but it is unlikely that we could ever understand the mind and heart, which never stop, no matter how many of these still images we layered on top of each other.

If visual hallucinations caused by brain tumors comprise an amenable area for scientific exploration and development, is not gaming disorder an unamenable area? If this is the case, then it is not surprising that research on endogenous schizophrenia, which lies between the two, has been difficult.

Jaspers' emphasis on the severing of the semantic continuum of life development and Schneider's first-class symptoms indicate that incidents are occurring not in the tool function itself, but in its users. Tool functions such as vision and hearing are markedly similar to the structure of a camera or microphone; for example, a crystalline lens and eye lens, or a tympanic membrane and diaphragm. However, what Jaspers and Schneider pointed out was not a malfunction of the camera or microphone, but a change in the gaze of the camera, and a change in the way the ear hears the sound picked up by the microphone. It would be very meaningful to consider whether the methods used to elucidate the modulation of the user who freely manipulates tool functions, i.e., the subject, consciousness, and ego, can be the same as the methods used to examine the tools themselves.

The incomprehensibility described by Jaspers is sometimes misunderstood as "the impossibility of understanding". The incomprehensibility by Jaspers means that the recollection of the experience using the grammar of the mind, which we normally do when we listen to the experiences of others, is

interrupted, and thus has nothing to do with whether the content is incomprehensible. It is tempting to jump to the conclusion that if it does not follow the grammar of the mind, it must be the brain, but it may be worthwhile to hold off. This is because in the Wilson-Cowan model of computational neurology, there is a break in the continuity of outputs depending on the conditions of the coefficients (the input software, not hardware called the brain) (Fig. 4) 4). This suggests that the semantic continuity that Jaspers emphasized may be severed only by the encounter (input information) with a specific experience (event) rather than the brain (matter).

Conflict of Interest

Itokawa, Arai, and Miyashita have a conflict of interest with Kowa Company, Ltd. regarding the patent and development of pyridoxamine.

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Notes

*Gerrymandering: The practice of intentionally raising or lowering the disparity of votes to modify redistricting and make the election more favorable to one's party is called the gerrymandering technique. It was named after the electoral districts arbitrarily redrawn by Elbridge Gerry, then governor of Massachusetts, U.S.A., in 1812, which were in the shape of four great spirit salamanders. Changes in normal blood pressure and blood glucose levels can cause tens of thousands of new patients.

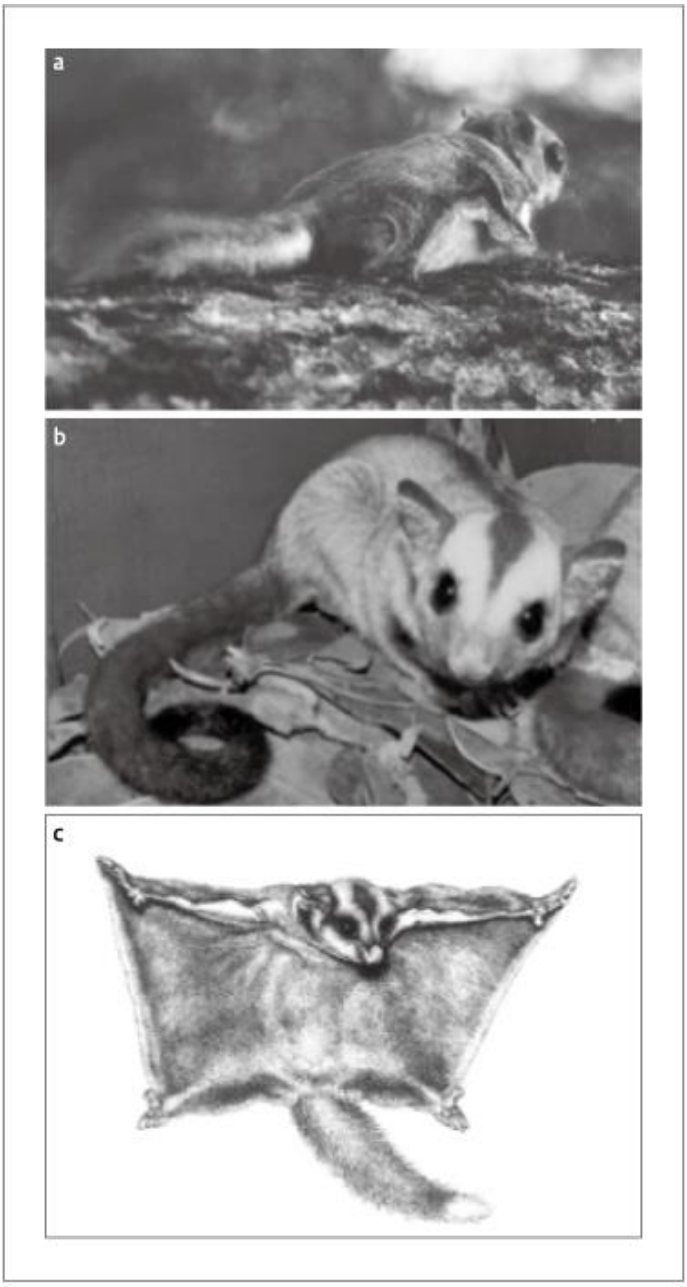

Figure 1: The flying squirrel and sugar glider
a: Siberian flying squirrel (*Pteromys volans*) (cited from Ref. 18), b: Mahogany glider (*Petaurus gracilis*) (cited from Ref. 3), c: Flying Mahogany glider (cited from Ref. 8). Figures a and b were modified by the author by reversing the left and right images and correcting the brightness.

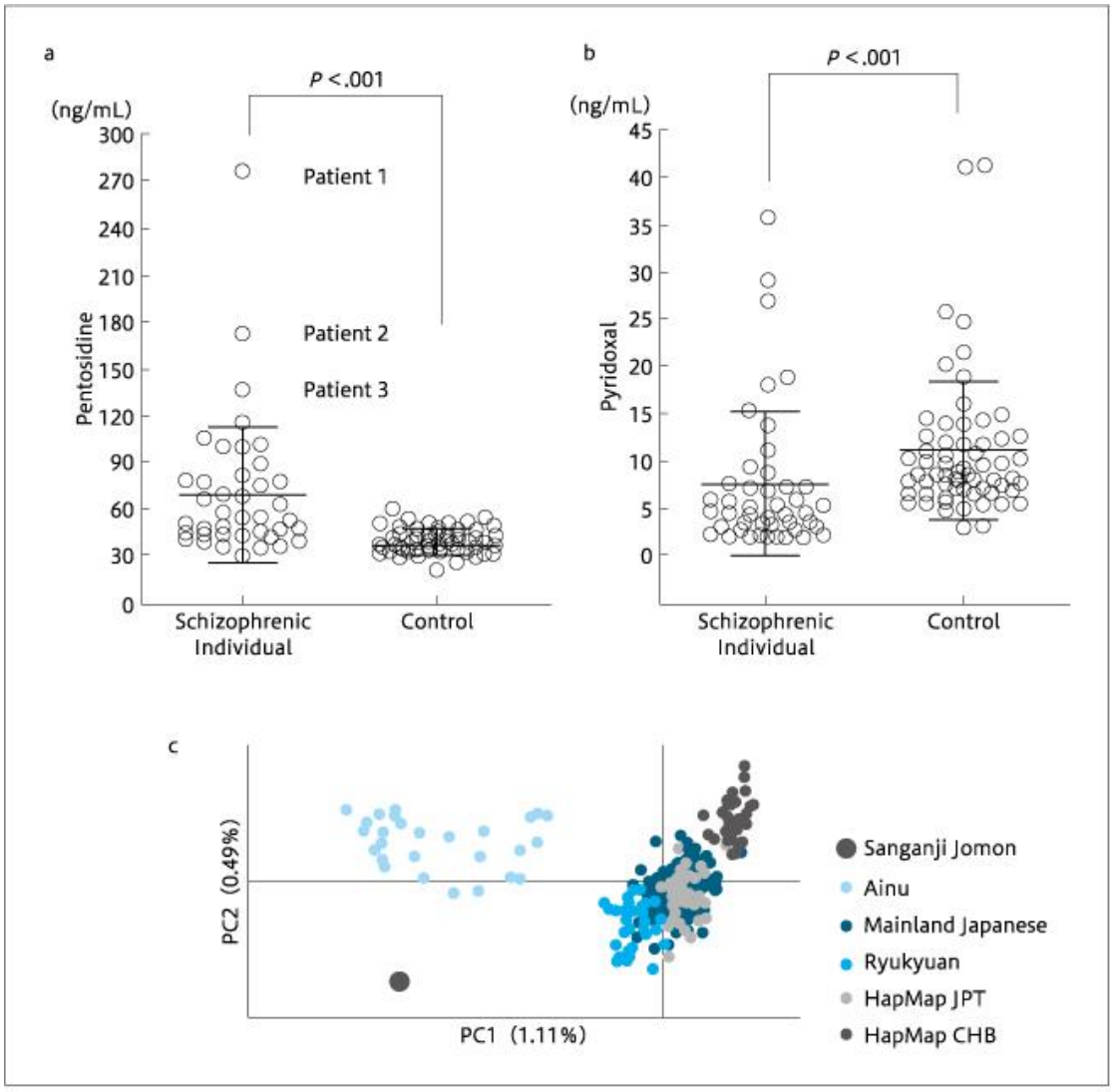

Figure 2 Graphs of types (a, b) and species (c)

a: Pentosidine (AGEs), b: Vitamin B6, values measured in schizophrenia and healthy controls, respectively. Symbolic figures that represent the difficulty of biomarker research for a type. The search for species in a huge type can be likened to digging up a gemstone buried in a sand dune. However, when we actually started our research, we found that what was buried in the sand dune was not a gemstone but mud dumpling. Values indicative of disease were continuous with normal values, as if the margins were fragile and easily assimilated into the sand. (Adapted from Ref. 2)

c: Human genome structure in Japan and neighboring regions: Human genome structures in Honshu, Japan, Ryukyu, and Beijing, China, are in close contact with each other, and there is continuity within the typology of Oriental people. On the other hand, the Ainu and Jomon show a discontinuous cluster from these clusters

and can be positioned as a separate species from the Honshu and Beijing humans in terms of genome structure. (Adapted from Ref. 9)

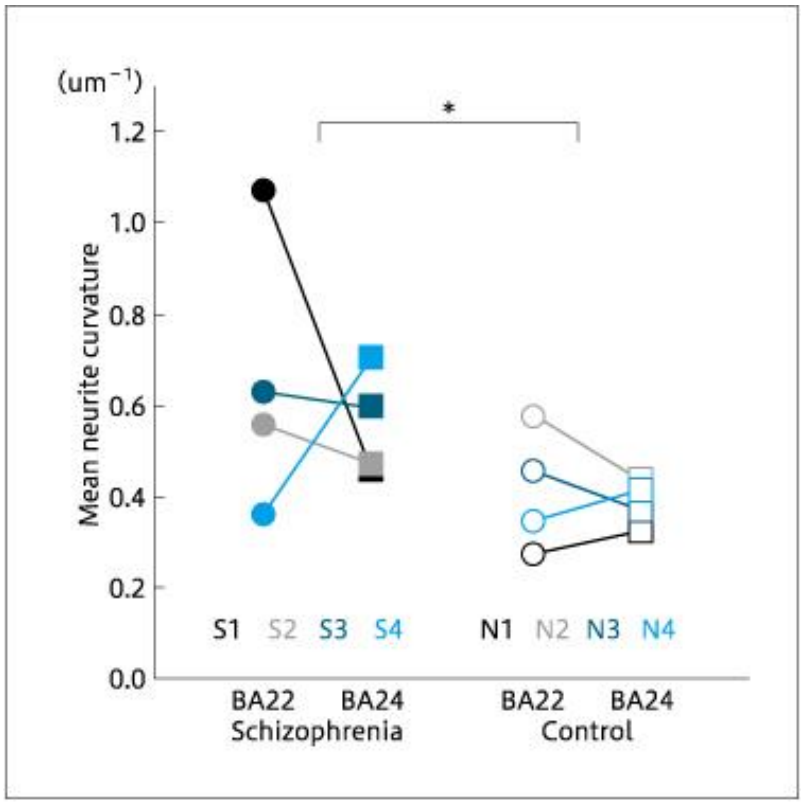

Figure 3 Neurite curvature in postmortem brain
S1-S4: schizophrenia, N1-N4: control, curvature of neurites in the superior temporal gyrus (BA22) and anterior cingulate gyrus (BA24) are different within the same individual. The curvature of neurite curvature also differed between schizophrenics and controls. (Adapted from Ref. 13).

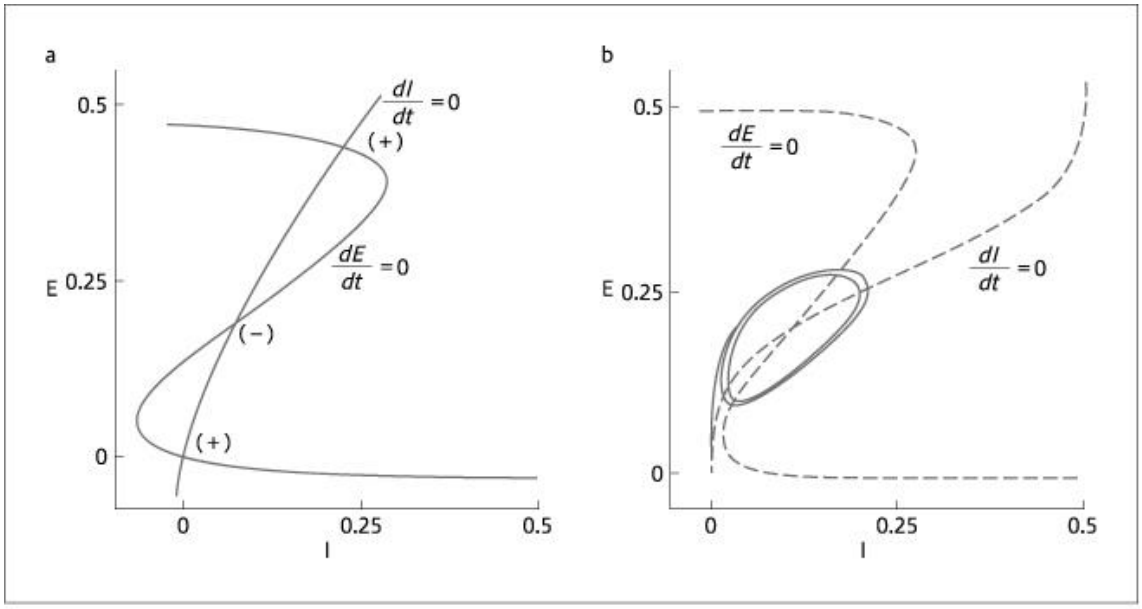

Figure 4 Wilson-Cowan model and limit cycle

In the following differential equation, where E(t) is the behavior of the excitatory nerve and I(t) is that of the inhibitory nerve, under the condition that wEE = 12, wEI = 4, wIE = 13, wII = 11, hE(t) = 0, and hI(t) = 0, the intersection of the two curves is in equilibrium, the (+) point is stable, and (-) point is unstable (a). Thus, no matter where one starts in the phase diagram, the nervous system converges to one of the two stable (+) points. However, if wEE = 16, wEI = 12, wIE = 15, wII = 3, hE(t) = 1.25, and hI(t) = 0, the stable intersection point disappears and the system continues to circle around the central closed orbit (limit cycle) (b). In other words, the activities of E and I never converge to a stable equilibrium point in the system as a whole.

τ dE/dt = -E(t) + (1-rE(t))fE[wEEE-wEII + hE(t)
τ dI/dt = -I (t) + (1-rI (t)) fI [wIEE-wIII + hI (t)].

Assuming that a is normal information processing (the greatest common denominator judgment of the society to which one belongs = the behavior of reaching a stable point), b is a state in which the greatest common denominator stable point is not reached, and the situation in which a wide range of information (= the initial state) results in an unstable circle (= the limit cycle) is analogous to "everything in the world affects me" (Konrad) and Antefestum's situational agnosia (Bin Kimura) in the apophenic period. The change from a to b is discontinuous and can be an analogy for the severance of the semantic continuity of Jaspers. fMRI data from 42 healthy subjects were analyzed in the Wilson-Cowan model during a stimulus task.

Although there is a previous study that analyzed fMRI data from 42 healthy subjects with a stimulus task using the Wilson-Cowan model, it only examined the causal coupling of the components of the brain system 19). There have been no empirical studies on humans or primates that have examined the Jaspers' Verstehen and limit cycle.
(Adapted from Ref. 4)