**Editorial**

# Psychopathology of the 21ˢᵗ Century: Application to Schizophrenia

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## Editorial

Inspired by Barrios' classification of psychopathology (descriptive, experimental and psychodynamic) [1], psychopathology can be expanded into the following 4 subtypes [2]:

1. **Qualitative psychopathology (descriptive, phenomenological):** focus on the form of symptoms. Examples: types of hallucinations (auditory and visual), types of delusions (paranoid, somatic, grandiose…etc.).

2. **Quantitative (numerical) psychopathology:** assigning numbers to symptoms and signs. Example: Duration of auditory hallucination: (1) < 1 hour, (2) 1-4 hours, or (3) > 4 hours per day. Quantitative psychopathology is useful in measuring severity of symptoms, efficacy of treatment, hypothesis testing and other research inquiries.

3. **Etiological psychopathology:** focus on the causes of symptoms. Are auditory hallucinations due to PTSD or a brain tumor?

4. **Experimental psychopathology:** the study of the relationship between an individual's psychopathology and objective measures such as hormone level or a brain imaging procedure.

### Failure of the disease model of Schizophrenia during the 20ᵗʰ century

At the turn of the twentieth century, Kraepelin conceptualized the disease model of dementia praecox (schizophrenia) and his classification model was enshrined in Western psychiatry for more than a century [3]. The disease model of schizophrenia included three core symptoms (delusions, hallucinations and disorganized thoughts) that were included in all diagnostic systems because they were the most frequently reported by patients [4]. The inclusion of three different groups of symptoms into the disease model of schizophrenia goes against the tenet of the disease model of classification because two patients with totally different symptoms can have the same diagnosis. In 1970, Robins and Guze published a seminal article proposing five phases of achieving valid classification of mental disorders: clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study [5]. The main point of Robins and Guze evidence-based approach is to create homogeneous groups so that researchers and clinicians can study etiology, pathogenesis, and treatment. The DSM diagnostic criterion for schizophrenia, which follows the disease model, does not identify homogeneous populations because patients with different presentations satisfy the official criteria. That explains why after forty five years, the Robins and Guze approach did not solve the problem of classification of schizophrenia [6].

Another failed attempt to salvage the disease model of schizophrenia is the delineation of schizophrenia subtypes (paranoid, disorganized, catatonic, undifferentiated, and residual), which have shown to be unreliable and inconsistent over time [7]. Eventually, the DSM-5 dropped the schizophrenia subtypes altogether and replaced them with "schizophrenia spectrum." **The model of schizophrenia as one disease has failed researchers and clinicians over the span of the 20ᵗʰ century.**

### The 21ˢᵗ century and advances in neuroscience

If one wonders why it has taken psychiatry so long to discard a single disease model of schizophrenia, Keshavan et al. has the answer: the relative recency of developments in neuroscience [6]. During the last three decades of the 20ᵗʰ century, there has been an explosion in neuroscience and brain imaging techniques allowing scientists to study brain structures and function even at a cellular and molecular level. Structural imaging (CT, MRI), functional imaging (fMRI), Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), genomics, pharmacogenomics, biomarkers, endophenotypes, epigenetic modifications, genetic variants and translational neuroscience technologies are some examples. There are new advances in neuroscience that will lead to **"neuroscience-informed nosology"** [8,9]. Kendler used a broader term, **"scientifically based psychiatric nosology,"** which will guide researchers and clinicians toward new classification of psychosis and other mental disorders in the 21ˢᵗ century [10].

### The ABC road map of neuroscience-informed nosology

Today, most experts agree that schizophrenia is not one disease, but many distinct diseases with overlapping symptoms [11]. I think it is time to move away from the failing disease model of schizophrenia and march into experimental psychopathology research. Uncovering the biological bases of individual symptoms may prove to be as or more helpful than studying constellations of symptoms (syndromes) in order to understand the pathophysiology of the illness [12].

I opine that neuroscience-informed nosology contains three essential components (A, B, C):

**A. Core Psychopathology:** Mental health system exists because patients come to doctors with symptoms and signs; it is a starting point [13]. Until recently, the reliability of measurement of individual symptoms and signs has been neglected. With the

publication of the Standard for Clinicians' Interview in Psychiatry (SCIP), more than 180 symptoms and signs of adult psychopathology have been reliably measured [2,14,15]. More research is needed to identify reliable items for eating disorders, attention/deficit disorder and personality disorders.

Here is an example of a reliable psychopathology item:

| MC1. Auditory hallucinations: | kappa |
|---|---|
| Do you hear noises (like music, whispering sounds) or voices talking to you when there is no one around? | |
| Are the voices like a real voice or just thoughts in your mind? | |
| Do voices ask you to do things? | **0.9** |
| 0    Patient has no auditory hallucinations. | |
| 1    Patient has auditory hallucinations. | |
| 2    Patient has auditory hallucinations with command. | |

**B.    Experimental psychopathology:** The correlation of psychopathology and objective measures starts with individual item(s), followed by carefully selected groups of items in sequence.

**1.    One-item experimental psychopathology:** In psychosis, researchers start with patients with only one symptom, such as auditory hallucinations, and examine the correlation between auditory hallucinations and brain changes.

**2.    Selected two-item experimental psychopathology:** Researchers can select patients with two symptoms together (e.g. auditory hallucination and visual hallucination) and examine their correlations with brain changes.

**3.    Selected multiple-item experimental psychopathology:** After performing adequate one-item and two-item experiments, researchers may decide to examine the brain changes in patients with several symptoms such as tangentiality, delusions and auditory hallucinations.

As experimental psychopathology research advances, researchers can use the **epistemic iteration principle** [previously used by Chang [16] in the science of temperature and applied to psychiatric nosology by Kendler [10]]. **In essence, epistemic iteration is a scientific process with three sequential steps.** First, science is built on what has been done before. Second, science advances with a bottom up approach (one-item experiments, then two-item experiments, then multiple-item experiments). Third, as scientific knowledge accumulates successive iterations and revision of experiments leads to a better approximation of reality. Kendler proposed using epistemic iteration in scientifically based psychiatric nosology, leading to "more accurate approximations of the reality of psychiatric illness" [10].

**C.    Neuroscience-Informed Nosology:** based on the information generated from psychopathology experiments and epistemic iteration, researchers will eventually identify several diseases that constitute what we call the "schizophrenia spectrum" today.

Modern psychiatric nosology research in the 21st century is based upon experimental psychopathology research and has already yielded with promising results [17-21]. Measuring the symptoms and signs of psychopathology items reliably at the level of individual items and correlating them with the brain changes *in vivo* is the right approach to unveil the mystery of psychiatric disorders such as the "schizophrenia spectrum."

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