Chapter 3
Toward a Multidimensional Continuum Model of Functional Psychoses for Research Purposes

Michael S. Ritsner

Abstract Schizophrenia (SZ), schizoaffective disorder (SA), major depressive disorder (MDD) and bipolar disorder (BPD) are clinically heterogeneous conditions called "functional psychoses" (FP). The paradigm, underlying the current model of FP, was based on Kraepelinian dichotomy and was a practical starting point for the categorical classification of FP. Nevertheless, the concept is increasingly challenged by emerging data from modern research in the field of clinical, genetic epidemiology, molecular genetics, neuroscience and neurobiological studies. The literature suggests that, despite intensive efforts and progress towards more reliability in classification, no definite and causally relevant biological abnormalities have been identified to date. Because the underlying disease mechanisms are poorly understood it is difficult to define a biologically plausible classification of functional psychoses. Recent research findings support a multidimensional model for FP. This chapter describes proof-of-concept for the Multidimensional Continuum Model (MDC model) of functional psychoses for research purposes. It is based on *multi-dimensional parameterization* of the clinical-endophenotype-genetic domains with a *three-axis continuum* (distribution) of psychopathological and behavior patterns among FP-affected persons, their relatives and the general population, on a *hypothesis-free approach*, and on an *endophenotype strategy*. The MDC model provides a framework for research purposes, in particular, for the study of the interactions between clinical, neurocognitive, behavioral, brain imaging and other neurobiological representations of functional psychoses. Postulated common to functional psychoses etiological and pathogenetic mechanisms include at least four interactive hits: a genetic load hit ("genetic vulnerability"), a neurodevelopmental hit ("neuronal vulnerability"), a stress sensitization hit ("life stress vulnerability"), and a neurodegeneration hit. These hits were presented as a Multi-Hits Vulnerability Model of functional psychoses. Implications for future researches in this field are discussed.

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Abbreviations

BPD	Bipolar disorder
BPRS	Brief psychiatric rating scale
CGI-S	Clinical Global Impression Severity scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth edition
FP	Functional psychoses
HPA axis	Hypothalamic-pituitary-adrenal axis
HRQL	Health related quality of life
ICD-10	International Classification of Diseases and Related Health Problems. Tenth revision.
MDC model	Multidimensional continuum model of functional psychoses for research purposes
MDD	Major depressive disorder
MHV model	Multi-Hits vulnerability model of functional psychoses
PANSS	Positive and negative syndrome scale
SAD	Schizoaffective disorder
SZ	Schizophrenia

Statement of Conundrum

Functional psychoses (FP) or schizophrenia (SZ), schizoaffective (SAD), major depressive disorder (MDD) and bipolar disorder (BPD) vary widely in clinical presentation and course (onset, remission and relapse), genetic epidemiology and molecular genetics, neuroimaging and neurobiological findings. Indeed, the symptoms of FP are remarkably heterogeneous to the extent that two patients with the same diagnosis (SZ, or SAD, MDD and BPD) can display completely different symptom patterns. Standard guideline criteria of categorical classifications of functional psychoses (DSM-IV [1] and ICD-10 [2]) are widely accepted and have several distinct advantages [3]. Discrimination between FP cannot be soundly based on the phenomenology of psychosis or symptom clusters [4, 5]. Overall, the categorical approach continues to be the focus of much criticism; in particular, research based on the presumption of a single disease has produced weak findings that frequently fail confirmation in replication studies [6–17]. Indeed, many investigators have attempted to dissect the phenotype into homogeneous subtypes using molecular genetics and endophenotype approaches, but these attempts had limited success in

relating the categorical subtypes to biological markers, genetic factors, or treatment response (see reviews [18]).

Converging evidence from critical studies comparing categorical and dimensional models of psychosis demonstrated that symptoms and disease course, risk factors, endophenotypes, and putative neurobiological underpinnings are better explained in terms of continuous distributions [19] (*see review and more specific criticism in Chapter 1 in this volume and other chapters of this book*). It is clear that standard nomenclatures do not represent disease entities with separate etiologies or rather different facets of the same disease. However, a recently published draft of the DSM-V is based on the same categorical model of functional psychoses (http://www.dsm5.org/Pages/Default.aspx).

Thus, other conceptualizations of FP for research purposes are warranted. A promising and useful line of research for assessing the validity of competing definitions or continuum models in psychotic disorders is to establish a strategy that combines multidimensional and polydiagnostic approaches to define clinical markers or phenotypes [20]. As an initial step in this endeavor, Brown and Barlow [21] suggest introducing dimensional severity ratings to the existent diagnostic categories and criteria sets. Therefore, the most useful approach to classification seems to be the complementary use of categorical and dimensional representations of functional psychoses [22, 23]. Dutta and colleagues [24] consider that at present the best option is to implement a hybrid of a categorical-dimensional approach in DSM-V. This would introduce the benefit of increased explanatory power of clinical characteristics, without completely dismissing the traditional paradigm of the Kraepelinian dichotomy. The dimensional approach to classification of functional psychoses is not intended to substitute categorical organization but rather to complement it in clinical practice and to challenge the exclusivity of the categorical approach in research settings. Current data indicate that psychotic disorders are best understood dimensionally rather than categorically [25–27]. Setting the boundaries for psychosis is not a limiting problem in dimensional models as in categorical models, but whether or not there is a continuum from normality to psychosis is controversial. Current discussions about dimensional and categorical approaches, which both have value, and limitations, are presented [28]. *Nevertheless, no proposals have been offered for introducing dimensional classification in the diagnostic system in a valid and feasible manner*.

Recently, the National Institute of Mental Health (NIMH) included in its new Strategic Plan a specific aim to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [29]. This goal is being implemented with a new initiative dubbed the Research Domain Criteria project. The intent is to create a framework for research classifications that reflect functional dimensions stemming from translational research on genes, circuits, and behavior (http://www.nimh.nih.gov/research-funding/newsletter/2009-july-inside-nimh.html#message-from-the-nimh-director). Examples of such domains might include executive functioning, fear circuitry, and reward circuitry [30].

Proof-of-Concept for a Multidimensional Continuum Model

Basic principles applied to the conceptualization of a *Multidimensional Continuum Model* (MDC model) [31] of functional psychoses for research purposes include (see Fig. 3.1):

1. Recognizing a *three-axis continuum* that precedes the distribution of phenotypic dimensions of functional psychoses: *one axis* represents a phenotypic continuum among *FP-affected persons, second axis* – among *relatives of probands with* functional psychoses, and *third axis* – in the *general population* (Fig. 3.2). Variation within each continuum of psychotic experience has been recently discussed [32].
2. Using a *multidimensional approach* that allows us to assess all phenotypic expressions of functional psychoses such as psychopathological symptoms, aggressive and suicidal behaviors, insight, cognitive functioning, and health related quality of life, general functioning, side effects, neurobiological and other characteristics.
3. Using a *hypothesis-free (empirical) approach* for parameterization and classification of the phenotypic expressions of functional psychoses.

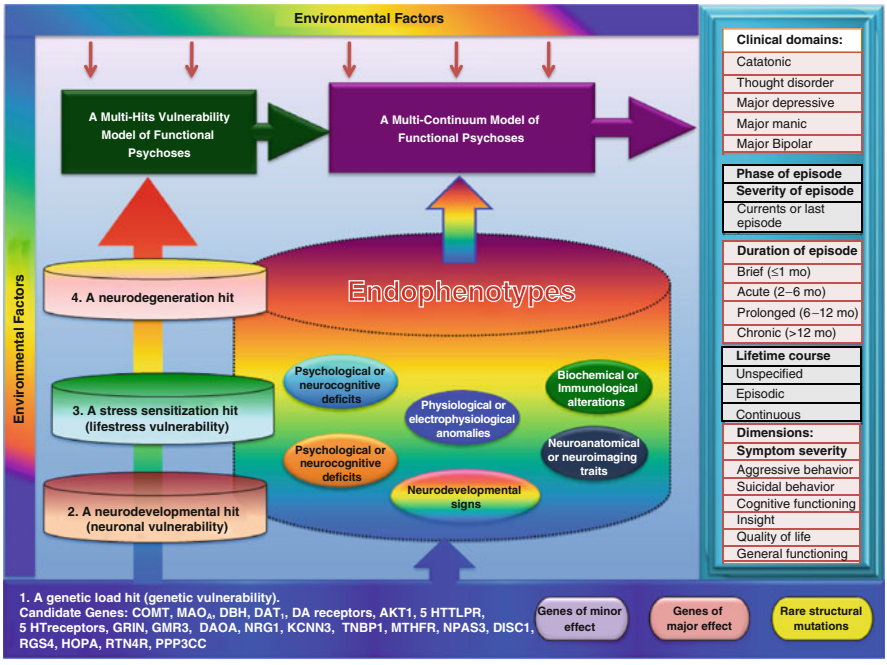


Fig. 3.1 Multidimensional continuum model of functional psychoses for research purposes (version 1.1). © M.S. Ritsner 2011 and used by permission

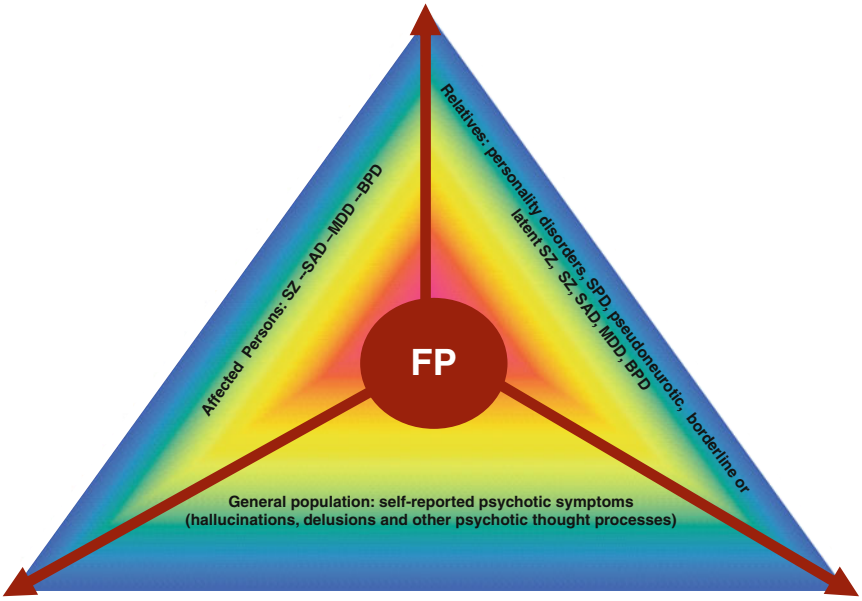


Fig. 3.2 A Three-axis continuum model of functional psychoses (FP). © M.S. Ritsner 2011 and used by permission

4. Using the *endophenotype approach* [33] for investigating gene-phenotypic relationships in order to define future typology of functional psychoses based on etiological and pathophysiological (neurobiological) mechanisms.
5. Recognizing *unitary etiological and pathogenetic components* underlying functional psychoses.

According to the MDC model each patient with functional psychoses may be characterized by the following parameters (Table 3.1):

(a) phase of episode,
(b) severity of episode,
(c) current or last episode,
(d) duration of episode,
(e) lifetime course, and
(f) phenotypic domains.

The dimensions of the phenotypic expression of current mental health state are assessed using psychiatric rating scales, a cognitive test battery and self-reported inventories: catatonic, positive and negative symptoms, aggressive and suicidal behaviors, depressive, anxiety, and mania symptoms, emotional and somatic distress, insight, cognitive functioning, health related quality of life (HRQL), general

Table 3.1 Measuring severity of phenotypic dimensions of functional psychoses

Parameters of phenotypic expression	Domains of functional psychoses				
	Catatonic domain	Thought disorder domain	Major depressive domain	Major manic domain	Major bipolar domain
Phase of episode	Acute (relapse), full (asymptomatic) or partial (asymptomatic) remission; unspecified. PANSS remission items may be considered according to their factor loadings [51, 122, 123]. Remission in SZ may be measured either by improvements in overall psychopathology from baseline (as measured by statistically significant percentage reductions in all thirty PANSS) items or by reduction below specific threshold levels (e.g.: scores of less than 3 in all thirty PANSS items) [124, 125]				
Severity of episode	Clinical Global Impressions Scale [126]. Based on work by Leucht and others [127–129], being considered "mildly ill" according to the CGI approximately corresponded to a PANSS total score of 58, "moderately ill" to a PANSS of 75, "markedly ill" to a PANSS of 95 and severely ill to a PANSS of 116. To be "minimally improved" according to the CGI score was associated with a mean percentage PANSS reduction of 19, 23, 26 and 28% at weeks 1, 2, 4 and 6, respectively. The corresponding figures for a CGI rating "much improved" were 40, 45, 51 and 53%				
Current or last episode	A prodromal episode, a single (or first) episode, a recurrent episode (number of episode)				
Duration of episode	Weeks or months				
Life time course	Unspecified, continuous, episodic				
Severity of symptoms	Bush-Francis catatonia rating scale [130]; Brief psychiatric rating scale [34], Positive and negative syndromes scale [35], Scale for the assessment of negative symptoms [131], Calgary scale for depression in schizophrenia [132], Hamilton depression scale [133]; Hamilton anxiety scale [126]; Bech-Rafaelsen mania rating scale [134], Clinician-administered rating scale for Mania [135]; Overt aggression scale [136], Life history of aggression scale [137]				
Insight (awareness)	Insight and treatment attitudes questionnaire [138], Scale to assess unawareness of mental disorder [139–141]				
Cognitive functioning	Cambridge automated neuropsychological test battery [142], Measurement and treatment research to improve cognition in schizophrenia [143], Mindstreams computerized cognitive test battery [144]				
Quality of life	Quality of life enjoyment and life satisfaction questionnaire [145], Heinrichs-carpenter quality of life scale [146], World Health Organization quality of life-bref scale [147, 148]				
General functioning	Global assessment of functioning scale [126]				
Side effects	Extrapyramidal symptom rating scale [149, 150], Barnes akathisia scale [151], Simpson-angus scale [152], abnormal involuntary movements scale, Distress scale for adverse symptoms [63]				

functioning and side effects. Some interview-based scales have been developed to measure the full range of psychiatric symptoms, such as the Brief Psychiatric Rating Scale (BPRS) [34] and the Positive and Negative Syndrome Scale (PANSS) [35], whereas other interview-based scales have been designed to tap specific dimensions, such as the Scale for the Assessment of Negative Symptoms (SANS) [36]. The same classification holds true for self-report scales. A battery of standardized psychometric scales should be administered to measure all these dimensions (Table 3.1). These and other (well-known or new) instruments should be validated, if possible, shortened and divided to 2–3 sets according to needs of different research purposes.

Phenotypic domains: There is wide agreement among psychiatrists and biological researchers that functional psychoses are a multi-dimensional spectrum of broadly heterogeneous disorders, but there is less consensus concerning the number and types of disorders. My research and clinical experience of treating patients with functional psychoses over the last 30 years suggests that the functional psychoses continuum may be currently divided into five *phenotypic (clinical) domains:*

(a) catatonic,
(b) thought disorder,
(c) major depressive,
(d) major manic, and
(e) major bipolar.

At this stage, researchers may use some DSM-IV clinical criteria (Table 3.2) for domain representations in order to search for FP domains that will be based on *phenotypic dimensional-endophenotype-gene associations*.

Detailed discussion about each FP-domain is beyond the scope of this chapter; the reader is advised to refer to the other relevant chapters, however I do have a few comments.

- *Catatonia* is a motor dysregulation syndrome described by Karl Kahlbaum in 1874 who considered it an independent disease. Emil Kraepelin made it a linchpin of his concept of dementia praecox [37]. Catatonia is a distinct neuropsychiatric syndrome (non-malignant, malignant, a dream-like stupor) that is increasingly recognized both clinically and in ongoing research [38]. The DSM-IV recognizes catatonia as a distinct diagnostic category (catatonia due to organic mental disorder), a subtype of SZ, as an episode of MDD and BPD and in the framework of neuroleptic malignant syndrome. Catatonia was found in 10–38% of psychiatric populations. Fink [39] asked to divorce catatonia from SZ and to recognize catatonia as an independent diagnostic class in the forthcoming DSM-V. Clinicians developed rating scales to identify the catatonia syndrome and applied the immediate relief afforded by a barbiturate or a benzodiazepine as a diagnostic test, the lorazepam test. Heckers and colleagues [40] mentioned three compelling reasons to change the classification of catatonia in the next edition of

Table 3.2 Definition of functional psychoses domains in the terms of DSM-IV [1]

FP-domains	Included (DSM-IV codes)	Excluded
Catatonic domain	Schizophrenia, catatonic type (295.20)	Catatonic disorder due to general medical condition (293.89); catatonia in framework of neuroleptic malignant syndrome
Thought disorder domain	Schizophrenia (295.1, 295.3, 295.6, 295.9), schizophreniform disorder (295.4), schizoaffective disorder (295.7), delusional disorder (297.1), brief psychotic disorder (298.8), shared psychotic disorder (297.3); MDD and BPD with mood-incongruent psychotic features.	Schizophrenia, catatonic type (295.20); alcohol-induced psychotic disorder with hallucinations (291.3) and with delusions (291.5); substance-induced psychotic disorder with delusions (292.11) and with hallucinations (292.12); psychotic disorder due to general medical condition with delusions (293.81) and with hallucinations (293.82)
Major depressive domain	Major depressive disorder, single episode (296.2x) and recurrent episode (296.3x); bipolar II disorder (296.89)	Major depressive episode with mood-incongruent psychotic features; dysthymic disorder (300.4); alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7)
Major manic domain	Bipolar I disorder with manic episode (296.0x)	Manic episode with mood-incongruent psychotic features; alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7); cyclothymic disorder (301.13); bipolar II disorder (296.89)
Major bipolar domain	Bipolar I disorder with most recent episode manic (296.4x), mixed (296.6x) and depressed (296.5x) At least two episodes (one manic and other depressive) should be documented.	Major depressive, manic, and mixed episodes with mood-incongruent psychotic features; bipolar II disorder (296.89); alcohol-induced mood disorder (291.8); substance-induced mood disorder (292.84); mood disorder due to general medical condition (293.83); bipolar I disorder with most recent episode hypomanic (296.40) and unspecified (296.7); cyclothymic disorder (301.13)

the DSM: (1) catatonia is often not recognized, (2) a better recognition of catatonia would facilitate proper treatment, and (3) a better recognition of catatonia as a diagnostic entity would catalyze the dormant research of the neural and genetic mechanisms of catatonia. Authors claim that removing catatonic symptoms as a diagnostic feature of schizophrenia from the DSM would affect the classic phenotype of SZ. However, "the classic phenotype of SZ" has already been affected by many clinical, epidemiological, genetic and neurobiological studies [7–17, 41–43].

- The *thought disorder domain* exhibits widely diffuse positive symptoms (marked delusions with or without hallucinations) with disturbances of emotion and a broad range of negative symptoms, cognitive decline, HRQL and functional impairments with personality deterioration. Following Jaspers' hierarchical principle stating that "schizophrenic" symptoms have diagnostic prominence over "mood" symptoms for diagnostic and prognostic purposes [44] the MDC model suggests including in this domain patients with depressive and manic episodes with *mood-incongruent psychotic features*. Accordingly, such patients should be excluded from the major depressive domain, the major manic domain and from the major bipolar domain.
- Furthermore, the presence of a *mania episode* in the absence of depressive episodes is insufficient for a diagnosis in the *major bipolar domain*. Lastly, dysthymic and cyclothymic disorders should be removed from FP since they are characterized by chronic, *non-psychotic mild signs and symptoms*.

Thus, preliminarily, a "diagnosis" for research purposes of a person with functional psychosis could be characterized by clinical domain (*catatonic, thought disorder, major depressive, major manic or major bipolar*) domain, phase of episode, severity of episode, current or last episode, duration of episode, life time course, and specific measures of the phenotypic expressions (Table 3.1).

Symptom Dimensions

The emerging dimensional approach to classification and treatment of psychiatric disorders calls for better understanding of diagnosis-related variations in psychiatric syndromes and for proper validation of psychometric scales used for the evaluation of those syndromes. The PANSS is a well-established rating scale used in the research of schizophrenia and related disorders. Findings from this rating scale are usually presented as mean scores (total and/or sub-scales), nevertheless, raw scores include much more information such as symptom severity, factor structure, symptom frequency and patterns. Psychotic symptoms such as hallucinations and delusions, disorganized speech and behavior, and negative symptoms are distributed along a continuum that extends from SZ to psychotic mood disorders with increasing levels of severity [45]. For the translation of research results into practice, understanding of the PANSS scores from a clinical perspective is essential.

Factor Structure: The study of symptom structure serves two main purposes in the field of psychopathology research. First, the identification of consistent patterns of symptom clusters may help identify homogeneous subgroups of patients and provide validation for diagnostic concepts. Second, distinct clusters may hypothetically reflect distinct pathophysiologies within the schizophrenic disorder [46, 47]. The symptoms of FP aggregate in factors. Different factor structures with solutions have been found using exploratory factor analyses on the PANSS. Regarding the number of putative dimensions underlying psychosis, there is some consensus that there are 3–7 factors underlying the latent structure of psychosis: reality distortion, disorganization, negative symptoms, catatonia, mania, and depression. Several symptom dimension models were constructed for SZ from the 30 PANSS items:

1. a three-factor model was established with positive, negative, and general psychopathological scale scores [48].
2. five-factor models with (a) anergia, thought, activation, paranoid, and depression factors or clusters [48]; (b) negative, positive, cognitive, excitement and depression components [49, 50]; and (c) negative factor, positive factor, activation, dysphoric mood and autistic preoccupation [51].
3. Van den Oord et al. [52] revisited the factor structure and external validity of the PANSS in a sample of 500 participants with DSM IV diagnoses of schizophrenia. They found that five factors corresponded closely to those typically derived in other studies: Negative, Positive, Excited/Activation, Anxious-Depressed/Dysphoric, and Disorganized/Autistic preoccupation, while the sixth factor seemed to have face validity and was labeled Withdrawn. With the exception of Anxious-Depressed/Dysphoric, Cronbach's Alpha ranged from 0.70 to 0.85 suggesting an acceptable internal consistency.
4. Six- and seven factor solutions have also been reported [51, 53].

There is evidence based on the use of exploratory factor analysis of the PANSS in heterogeneous populations of patients with FP. Purnine and associates [54] examined the reliability and validity of PANSS among outpatients with schizophrenia (N = 75) and mood disorders (N = 61). Four of five factors were similar to those reported among inpatients with schizophrenia. Daneluzzo and collegues [55] compared the clinical characteristics of manic patients with those of SZ patients evaluated with PANSS. The clinical symptoms of 148 BPD patients and 86 SZ patients hospitalized for an index psychotic episode were assessed. Schizophrenic patients showed more positive and cognitive symptoms than BPD. The factor analysis of the two PANSS scores showed a three-factor solution with "positive", "negative" and "mixed" depressive-activated factors for BPD and "positive", "negative" and "depressive" factors for SZ. Factor analysis in a large sample (N = 1,294) of patients diagnosed with DSM-IV schizophrenia (n = 460), BPD (n = 726) and delusional disorder (n = 108) subjects indicated that the symptomatology of major psychoses is composed of the following five factors: mania, positive symptoms, disorganization, depression and negative symptoms [56]. Eisenberg and associates [57] administered the PANSS to subjects with SZ (n = 305), organic brain disease

(n = 66) and major depressive disorder (MDD, n = 75). The results of this study indicate diagnosis-related variations in the negative and depressive syndrome dimensions in schizophrenia, organic brain disease and MDD. These results also validate limited use of the PANSS for evaluation of negative and depressive syndromes in disorders other than schizophrenia. Overall, this data suggested that positive, negative, and disorganization factors are not specific to SZ; this is consistent with a dimensional view of psychopathology in FP [58]. Finally, Rietkerk et al. [59] investigated whether the symptom dimensions "reality distortion", "psychomotor poverty" and "disorganization" are heritable phenotypes. Data from twin and affected sibling studies are consistent with a genetic contribution to the disorganization dimension. These data suggest that only the disorganization symptom dimension may provide a useful alternative phenotype for genetic research. Additional research is necessary to reach definitive conclusions.

Symptom Frequency, Numbers and Patterns (Fig. 3.3): PANSS item raw scores are not particularly helpful for norm-referenced interpretation. *A raw score of 3 and more for each PANSS item may be used as a cutoff for a clinically relevant symptom*. Thus, we can progress from symptom (item) severity to symptom frequency, numbers and patterns that may lead us to categorical clinical presentation of mental health state of patient.

For instance, Fig. 3.4 shows the frequency of PANSS symptoms (defined as 3 and more raw scores) for 579 inpatients and outpatients with various severities

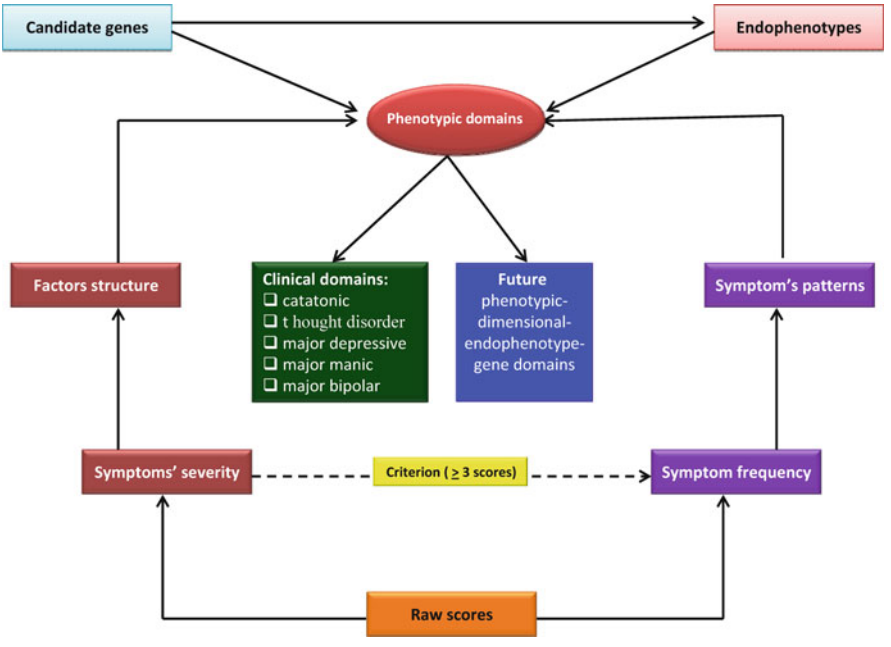


Fig. 3.3 Analysis of dimensional and categorical parameters are based on PANSS raw scores. © M.S. Ritsner 2011 and used by permission

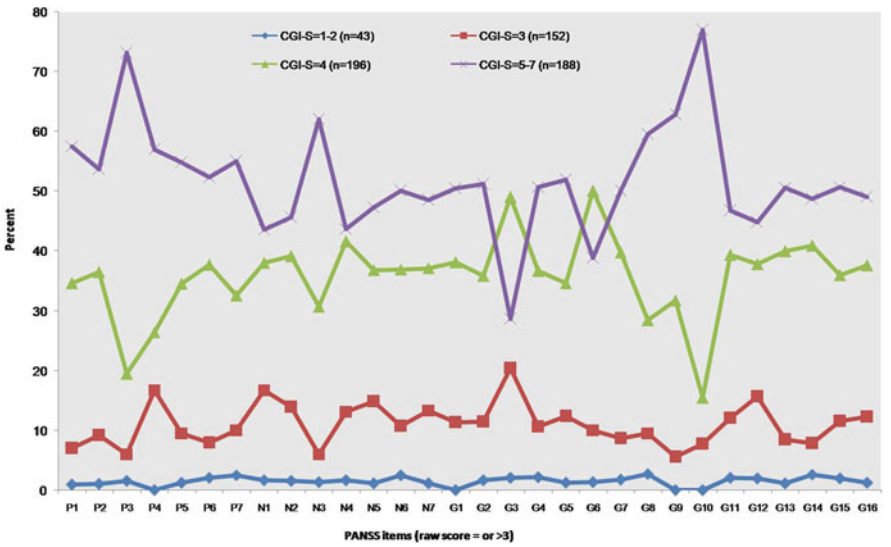


Fig. 3.4 Frequency of PANSS symptoms (defined as 3 and more row scores) among persons with various severities of functional psychoses measured by CGI-S

Table 3.3 Mean number of PANSS symptoms and DSM-IV diagnoses of 579 patients with functional psychoses

Severity of illness	Number of PANSS symptoms		Distribution of patients by DSM-IV diagnoses (codes)						
	Mean	SD	295.1	295.3	295.6	295.7	295.9	296	Total
CGI-S (1–2 scores)	1.6	4.2	0	29	10	1	0	3	43
CGI-S (3 score)	3.7	4.9	1	91	33	14	8	5	152
CGI-S (4 score)	8.9	5.4	7	100	28	35	8	18	196
CGI-S (5–7 scores)	12.7	5.0	13	120	21	20	8	6	188
Total	–	–	21	340	92	70	24	32	579

CGI-S – Clinical Global Impressions Scale: 0 = Not Assessed; 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients

of functional psychoses as measured by CGI-S (Table 3.3). As can be seen, the higher the CGI-S scores the higher the frequency and the most PANSS symptoms. In addition, these findings might be presented as the "number of PANSS symptoms" (Fig. 3.5), and as individual patterns of symptoms (Fig. 3.6). These individual patterns look different than mean scores of five symptom factors (Fig. 3.7).

Temporal Stability: One potential challenge of the dimensional approach is the assumption that FP patients experience drastic symptom changes over time. For a

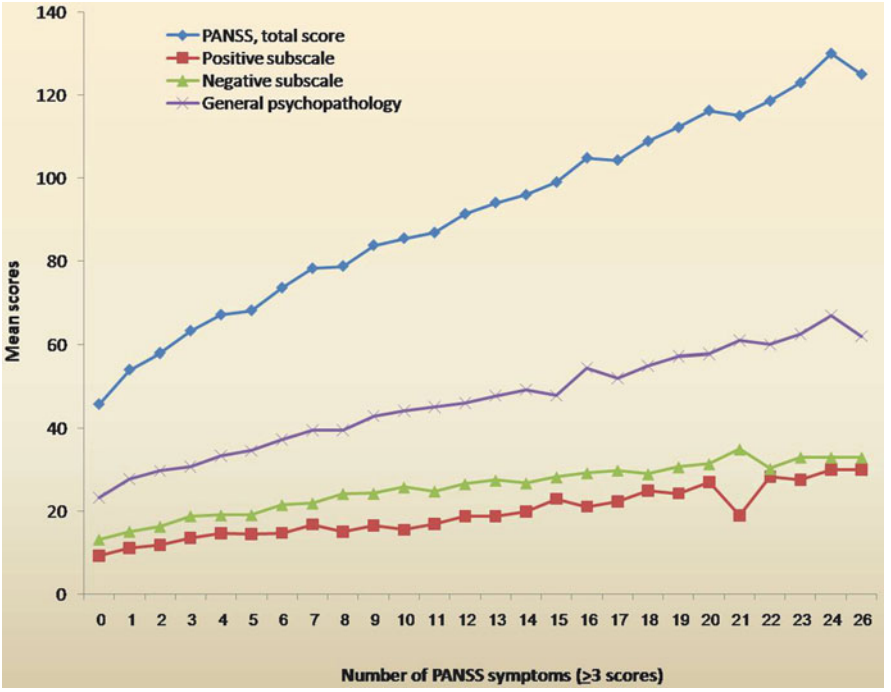


Fig. 3.5 PANSS positive, negative, general and total mean scores by number of symptoms among 579 patients with functional psychoses

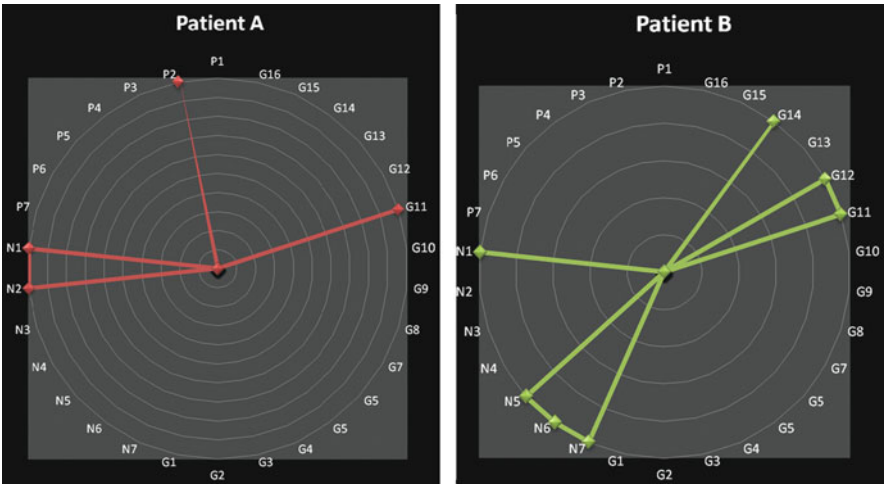
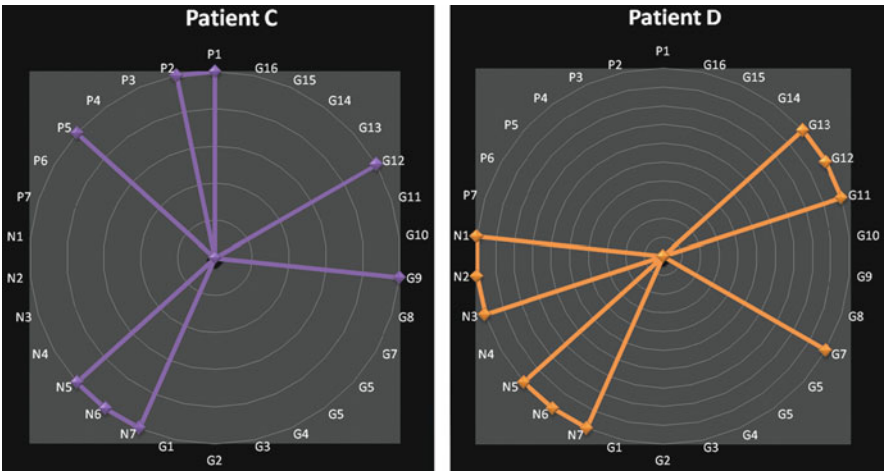
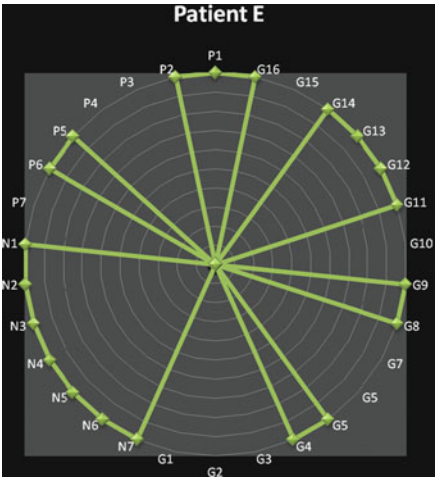


Fig. 3.6 Individual patterns of PANSS symptoms among persons with functional psychoses. PANSS items: positive: P_1–P_7, negative: N_1–N_7, and general psychopathology: G_1–G_{15}





Patients	Sex	Age (yr.)	DSM-IV	Illness duration (yr.)	CGI-S, score	PANSS, score	Number of symptoms
A	Men	37	295.3	9	3	72	4
B	Men	42	295.6	17	4	82	7
C	Men	23	295.3	6	4	83	8
D	Women	29	295.3	10	3	92	10
E	Men	22	295.3	5	4	112	20

Fig. 3.6 (continued)

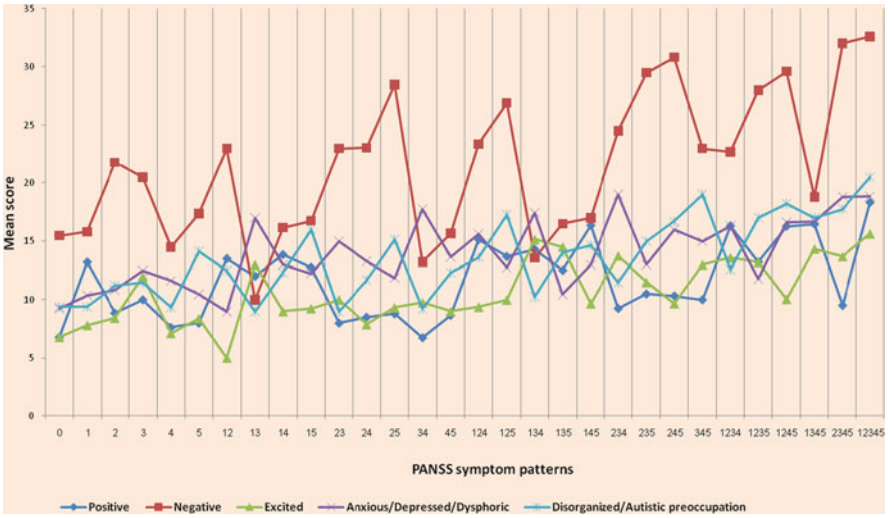


Fig. 3.7 Mean scores of PANSS factors by symptom patterns among 579 patients with functional psychoses. *Factor structure*: Positive factor (P_1, P_2, P_5, P_6, G_9), Negative factor (N_1:N_4, N_6, G_5, G_7, G_{13}, G_{16}), Excited or activation factor (P_4, P_7, G_4, G_8, G_{14}), Mood (anxious depressed/dysphoric) factor (G_1:G_3, G_6, G_{12}, G_{15}), Disorganized or autistic preoccupation factor (P_3, N_5, N_7, G_{10}, G_{11}, G_{13}). *Symptom patters*: 0 = all PANSS items ≤3 scores; 1 = Positive factor symptoms (at least one from P_1, P_2, P_5, P_6, G_9 items > 3 scores); 2 = Negative factor symptoms (at least one from N_1:N_4, N_6, G_5, G_7, G_{13}, G_{16} items > 3 scores); 3 = Excited factor symptoms (at least one from P_4, P_7, G_4, G_8, G_{14} items > 3 scores); 4 = Mood factor symptoms (at least one from G_1:G_3, G_6, G_{12}, G_{15} items > 3 scores); and 5 = Disorganized factor symptoms (at least one from P_3, N_5, N_7, G_{10}, G_{11}, G_{13} items > 3 scores). Consequently, for instance, pattern 12 includes Positive and Negative symptoms; pattern 235 means Negative-Excited-Disorganized symptom pattern, and ctr

dimensional approach to be useful, some degree of symptom stability would be expected, but few longitudinal studies examined the evolution of symptoms per se. In a longitudinal study of symptoms, Arndt et al. [60] found that the negative symptoms were already prominent during the patients' first episode and remained relatively stable throughout the 2 years of follow-up. The positive symptoms of disorganization and psychoticism were found to be prominent at intake and declined over the course of the follow-up period. Repeat examinations of patients revealed results that further support the validity, internal consistency and inter-rater reliability of the five-factor models of SZ psychopathology as measured by the PANSS [50, 61, 62]. Reichenberg et al. [47] examined the stability of symptoms of SZ over time, focusing on the stability of symptom structure. Symptoms were assessed with the PANSS of 215 chronic patients followed up for as long as 4 years. The results demonstrate that despite changes in the severity of symptoms in individual patients with SZ, the factor structure and interrelatedness of symptoms have considerable stability over time.

The results long-term study [63, 64] of 108 patients that met DSM-IV criteria for SZ or SAD for 10-year period demonstrate a reduction in PANSS total scores

Table 3.4 Frequency of PANSS symptoms (scores ≥3) among 108 patients with schizophrenia and schizoaffective disorders at initial assessment and over 10-year follow up

		Initial assessment		10-year follow up assessment			
	Variables	*n*	%	*n*	%	χ^2 test	*p*
P1	Delusions	41	38.0	28	25.9	3.6	0.058
P2	Conceptual disorganization	50	46.3	35	32.4	4.4	0.036
P3	Hallucinatory behavior	16	14.8	13	12.0	0.4	0.55
P4	Excitement	17	15.7	12	11.1	1.0	0.32
P5	Grandiosity	15	13.9	16	14.8	0.04	0.85
P6	Suspiciousness	37	34.3	28	25.9	1.8	0.18
P7	Hostility	11	10.2	1	0.9	8.8	0.003
N1	Blunted affect	60	55.6	84	77.8	12.0	0.0005
N2	Emotional withdrawal	57	52.8	46	42.6	2.2	0.13
N3	Poor rapport	33	30.6	17	15.7	6.7	0.009
N4	Passive/apathetic	44	40.7	42	38.9	0.1	0.78
N5	Difficulty in abstract thinking	63	58.3	68	63.0	0.5	0.49
N6	Lack of spontaneity	45	41.7	31	28.7	4.0	0.046
N7	Stereotyped thinking	65	60.2	48	44.4	5.4	0.020
G1	Somatic concern	16	14.8	22	20.4	1.1	0.28
G2	Anxiety	29	26.9	7	6.5	16.1	0.0001
G3	Guilt feelings	.7	6.5	11	10.2	1.0	0.32
G4	Tension	34	31.5	4	3.7	28.7	0.0001
G5	Mannerism and posturing	27	25.0	5	4.6	17.8	0.0001
G6	Depression	14	13.0	16	14.8	0.2	0.69
G7	Motor retardation	10	9.3	7	6.5	0.6	0.45
G8	Uncooperativeness	13	12.0	5	4.6	3.9	0.049
G9	Unusual thought content	33	30.6	17	15.7	6.7	0.009
G10	Disorientation	4	3.7	3	2.8	0.2	0.70
G11	Poor attention	37	34.3	21	19.4	6.0	0.014
G12	Lack of judgment and insight	64	59.3	55	50.9	1.5	0.22
G13	Disturbance of volition	52	48.1	19	17.6	22.8	0.0001
G14	Poor impulse control	22	20.4	19	17.6	0.3	0.60
G15	Preoccupation	39	36.1	18	16.7	10.5	0.001
G16	Active social avoidance	56	51.9	22	20.4	23.2	0.0001

(p=0.044), and general psychopathology (p=0.008). Ratings of negative and positive symptoms did not change significantly during the follow-up period. When frequency of PANSS items (scored ≥3) was analyzed, two groups of symptoms were found (Table 3.4):

- *Groups of patients with stable frequency of symptoms* [delusions (P_1), hallucinatory behavior (P_3), excitement (P_4), grandiosity (P_5), suspiciousness (P_6), emotional withdrawal (N_2), passive/apathetic (N [4]), difficulty in abstract thinking (N_5), somatic concern (G_1), guilt feelings (G_3), depression (G_6), motor

retardation (G_7), disorientation (G_{10}), lack of judgment and insight (G_{12}), poor impulse control (G_{14}), active social avoidance (G_{16})]; and

- *Groups of patients with decreased frequency of symptoms* [conceptual disorganization (P_2, $p = 0.036$), hostility (P_7, $p = 0.003$), poor rapport (N_3, $p = 0.009$), lack of spontaneity (N_6, $p = 0.046$), stereotyped thinking (N_7, $p = 0.020$), anxiety (G_2, $p<0.001$), tension (G_4, $p<0.001$), mannerism and posturing (G_5, $p<0.001$), uncooperativeness (G_8, $p = 0.049$), unusual thought content (G_9, $p = 0.009$), poor attention (G_{11}, $p = 0.014$), disturbance of volition (G_{13}, $p<0.001$) and preoccupation (G_{15}, $p = 0.001$)]. Only frequency of blunted affect (N_1) was increased from 55.6% at initial assessment to 77.8% after 10-year period ($p = 0.0005$).

Thus, these dimensions have considerable validity and temporal stability. Longitudinal studies that followed patients from childhood to adulthood are needed to further understand the course of FP symptoms over longer periods of time.

Subtyping FP into mutually exclusive entities could be an endless process and would have the same limitations as some of the categorical approaches. A dimensional continuum model of FP provides researchers with a more complete picture. Because monosymptomatic patients are rare, dividing FP into mutually exclusive DSM-IV illnesses is unreasonable and impractical. From a dimensional perspective, each patient can score in one or more symptom dimensions. The focus is on symptom severity, frequency, profile or patterns. FP research should concentrate on identifying the general and specific etiological factors that contribute to the development of phenotypic domains. A dimensional approach assumes that FP symptoms are normally distributed in the general population. Future genetic endophenotype oriented studies involving patients from across a broad spectrum of FP or involving population-based samples may be particularly informative if phenotypic dimensions are stable traits.

Toward a Unitary Pathogenetic Mechanism

The etiology of FP is a topic of controversial debate, while researchers strive to achieve a common objective. The goal is to identify the cause(s) of FP to understand the complex interplay between environment and gene regulation. A conclusive identification of specific etiological factors or pathogenic processes in the FP has remained elusive, although recent studies have shown that several neurobiological alterations in domains of brain structure, physiology and neurochemistry may reflect diverse pathophysiological pathways from the "genome to the phenome" (see reviews [18, 65, 66]). The stress-vulnerability models of FP have dominated etiology theories for over three decades [67, 68]. For instance, the *neural diathesis – stress model* proposes that the constitutional diathesis for schizophrenia depends on neuroendocrine pathways through which stress exposure, specifically cortisol release mediated by the hypothalamic-pituitary-adrenal (HPA) axis, influences dopamine transmission [67, 69]. "Multiple hit" models suggested the importance of additive and interactive effects of environmental risk factors against a background

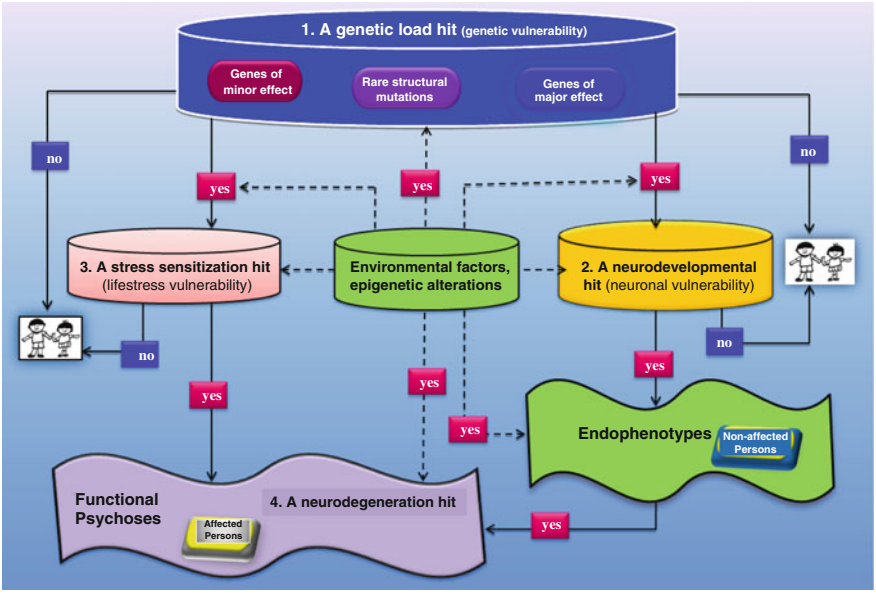


Fig. 3.8 A Multi-Hits Vulnerability Model of functional psychoses. © M.S. Ritsner 2011 and used by permission

of genetic predisposition [70–75]. Figure 3.8 presents the *Multi-Hits Vulnerability Model (MHV model)*, which based on interaction between four main hits:

(a) a genetic load hit ("genetic vulnerability"),
(b) a neurodevelopmental hit ("neuronal vulnerability"),
(c) a stress sensitization hit ("life stress vulnerability"), and
(d) a neurodegeneration hit.

A genetic load hit: For more than 40 years, researchers worldwide have sought to reveal the genetic basis of FP. Linkage and candidate gene association study results have led to a range of hypotheses concerning the pathogenesis of the disorders, but overall genetic findings have been inconsistent and not a single functional risk causing variant has been identified. Advances and challenges in molecular and genetic studies of FP were recently reviewed [18, 76–81]. Although linkage and association studies have identified a series of chromosomal regions likely to contain susceptibility genes, progress in identifying causative genes has been largely disappointing. However, rapid technological advances are beginning to lead to new insights. Systematic genome-wide association and follow-up studies have reported genome-wide significant association findings of common variants for schizophrenia and bipolar disorder. There is emerging evidence that some cases of FP (in particular, SZ) might be due to rare genetic structural variations, though the majority of cases are putatively due to a cumulative effect of common variations in multiple

genes, which in combination with environmental stressors may lead to the development of schizophrenia [82, 83]. The aggregate data provide support for polygenic inheritance and for genetic overlap in FP [79].

A neurodevelopmental hit: Owing to several advances, principally developments in neuroimaging, electrophysiological and neuropathological approaches, in the last two decades FP have been increasingly viewed as neurodevelopmental disorders [84–88]. Human epidemiological studies have provided compelling evidence that the risk of developing schizophrenia is significantly increased following prenatal and/or perinatal exposure to various environmental insults, including maternal exposure to stress, infection and/or immune activation, nutritional deficiencies and obstetric complications [89]. Pathways associated with genes that regulate neuronal migration by influencing the function of microtubules in the developing fetal brain may be interfered with as part of the "first-hit" of SZ [90]. There is evidence from brain pathology (enlargement of the cerebroventricular system, changes in gray and white matters, and abnormal laminar organization), genetics (changes in the normal expression of proteins that are involved in early migration of neurons and glia, cell proliferation, axonal outgrowth, synaptogenesis, and apoptosis), environmental factors (increased frequency of obstetric complications and increased rates of schizophrenic births due to prenatal viral or bacterial infections), minor physical anomalies, and gene-environmental interactions, which support of the neurodevelopmental model [18, 91–94]. In addition, findings from both cross-sectional studies of first-episode patients and longitudinal studies in childhood-onset and adolescent onset schizophrenia support the concept of early-onset schizophrenia as a progressive neurodevelopmental disorder with both early and late developmental abnormalities [95].

A stress sensitization hit: Psychosocial stress, such as life events, childhood trauma, or discriminatory experiences powerfully affect the brain and body and last throughout the entire life span, influencing brain function, behavior, and the risk for a number of systemic and mental disorders [96, 97]. There is evidence that environmental factors, which interact with multiple genes, and epigenetic factors, psychological or physiological alterations, induce persistent sensitization to stress [98, 99]. Stress sensitization may be critical in the development or relapse of FP. The neurobiological substrate of stress sensitization involves dysregulation of dopaminergic and noradrenergic systems.

Glutamatergic regulation activates HPA axis in stress response [67, 100]. The HPA axis is one of the primary neural systems triggered by stress exposure, in the expression of vulnerability for schizophrenia. The results indicate that psychotic disorders are associated with elevated baseline and challenge-induced HPA activity; that antipsychotic medications reduce HPA activation, and that agents that augment the stress hormone (cortisol) exacerbate psychotic symptoms (see review [68]). A fundamental question in the neuroendocrinology of stress-related psychopathology is why some individuals flourish and others perish under similarly adverse conditions. The data suggest that mineralocorticorticoid and glucocorticoid receptors contribute to individual differences in resilience and vulnerability to stressors [101]. Although many of the physiological effects of corticosteroid stress hormones on

neuronal function are well recognized, the underlying genomic mechanisms are only beginning to be elucidated [102]. Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress by undergoing structural remodeling, which alters behavioral and physiological responses. Lyons et al. [103] suggest that small hippocampi reflect an inherited characteristic of the brain of monkeys. It has been reported that volume reductions in the amygdala, hippocampus, superior temporal gyrus, and anterior parietal cortex common to both patient groups may represent vulnerability to schizophrenia, while volume loss of the prefrontal cortex, posterior parietal cortex, cingulate, insula, and fusiform cortex preferentially observed in schizophrenia may be critical for overt manifestation of psychosis [99]. Genetically informed clinical studies should assess whether inherited variation in hippocampal morphology contributes to excessive stress levels of cortisol through diminished neuroendocrine regulation. In humans with mood and anxiety disorders, small hippocampal volumes have been considered evidence that excessive stress levels of cortisol induce hippocampal volume loss. Translational studies in humans with structural and functional imaging reveal smaller hippocampal volume in stress-related conditions [104], and major depressive illness [105]. Laruelle [106] proposed that, in schizophrenia, neurodevelopmental abnormalities of prefrontal dopaminergic systems might result in a state of enhanced vulnerability to sensitization during late adolescence and early adulthood. It is also proposed that dopamine D_2 receptor blockade, if sustained, might allow for an extinction of this sensitization process, with possible re-emergence upon treatment discontinuation. Changes of protein expressions in the amygdala in the categories of synaptic, cytoskeletal, oxidative stress, apoptosis, and mitochondria related proteins could be associated with mechanisms underlying behavioral sensitization [107]. Behavioral sensitization to daily life (environmental) stress may therefore be a vulnerability marker for schizophrenia, reflecting dopaminergic hyper-responsivity in response to environmental stimuli [108]. There is evidence that emotional reactivity to daily life stress may be related to a familial liability to develop schizophrenia [109]. Stress sensitization is most often *unspecific for FP*, since its can trigger high blood pressure, diabetes, ulcers, asthma and digestive and lung ailments among others.

A neurodegenerative hit: has postulated that FP underlie progressive pathophysiological processes that occur in the brains of patients (see review [110]). The question of whether this key characteristic of the disorder means that schizophrenia is a degenerative disorder has been discussed for over 100 years [111]. Investigation of the long-term course of schizophrenia with progression to different residual syndromes has inferred that schizophrenia is not a neurodegenerative process in the usual sense, but may be uniquely neuroregressive in most cases [112]. The following findings support this assumption: 78% of SZ patients do not show full remitting courses; progression occurs only 5–10 years after onset; chronic defect psychoses can remit even after decades to non-psychotic pure deficiency syndromes; that approximately 15% progress even after years and decades of a remitting course and, finally, that altogether there is no correlation between the duration of course and outcome. There are associations between brain imaging and psychopathological

findings and also between the progression revealed in neuroimaging and psychopathological changes. Progressive MRI changes in longitudinal studies were revealed in childhood-onset SZ [113], before and after transition to psychosis [114], and in the course of early psychosis [115]. Progressive MRI changes were seen in subgroups of patients with chronic schizophrenia [116–118]. Some, though not all studies revealed more pronounced progressive brain changes in patients that are associated with poor outcome, more negative symptoms, and a decline in neuropsychological performance [119, 120]. Brain imaging studies documented progressive increases in ventricular size, accelerated loss of brain tissue, progressive delays in treatment response, and neurochemical (magnetic resonance spectroscopy) and neurophysiological (P300) indices, all of which are consistent with ongoing cerebral degeneration in a significant subgroup of schizophrenia patients [121].

Conclusions and Future Directions

Although emerging data from many fields of psychiatric research have increasingly challenged the validity of the DSM-IV and ICD-10 classifications, the categorical nosology of the functional psychoses needs further clarification for use in clinical practice. Since the current categorical nosology of functional psychoses challenges neurobiological studies, a new model and classification of FP for research purposes is needed.

This chapter describes proof-of-concept for the Multidimensional Continuum Model (MDC model) of FP for research purposes, that is based on multidimensional parameterization of the three-axis continuum of the phenotypic (clinical)-endophenotype-genetic domains, on a hypothesis-free approach, and on the endophenotype strategy. The complex clinical presentation of FP can be summarized with a few consistent, temporally stable symptom dimensions and factor structures. Although the factor structure of FP symptoms is imperfect, this quantitative approach to phenotypic traits has the potential to advance our understanding of FP and may aid in the identification of more robust endophenotypes. The Multidimensional Continuum Model is proposed for validation and further development. In particular, the first step towards this goal should be cross-sectional and longitudinal measures of phenotypic expressions of FP. Suggested observer-rated and self-report scales should be shortened and divided into 2–3 sets as per the various research purposes. Using a few consistent and temporally stable symptom dimensions, factors and patterns can summarize the complex clinical presentation of FP. A dimensional approach may advance our understanding of FP while symptom structure is far from definitive and is still subject to revision. Obviously, the FP domains mentioned above (catatonic, thought disorder, major depressive, major manic, and major bipolar) have been delineated to help elaborate future typology of FP that should be based on multidimensional measures of phenotypic expressions, endophenotypes and candidate genes. A further step would be to elaborate, for instance, a symptom profile of each FP-domain using raw scores of rating scales.

Multi-dimensional presentations of FP might stem from the interaction between four hits (a genetic load hit, a neurodevelopmental hit, a stress sensitization hit, and a neurodegeneration hit) as presented by the Multi-Hits Vulnerability Model. Further research is needed to determine common and distinct mechanisms for FP-domains. If supported, this model may have important implications for future classification of FP and much more effective treatment and rehabilitation. Ultimately such a classification should be based on an understanding of the etiology and pathogenesis of FP. Research on the common and distinct genetic and neural substrates of the various dimensions has already begun and is likely to develop even further.

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