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SPECIAL ISSUE

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The early course of schizophrenia and depression*

Abstract *Objective* Risk factors, emergence and accumulation of symptoms in the untreated early course were studied as a basis for understanding the relationship between schizophrenia and depression. *Materials and methods* 130 representative first admissions for schizophrenia were compared retrospectively with 130 individually matched first admissions for depressive episodes and with 130 healthy controls. *Results* Onsets of schizophrenia and severe depression were marked by depressive symptoms, followed by negative symptoms and functional impairment. This prodromal core syndrome became more prevalent as the disorders progressed, and it reappeared in psychotic relapses. Psychotic symptoms emerged late, indicating a different and more severe "disease pattern". *Conclusion* The prevalence of depressive symptoms in the general population and at the prodromal stage of numerous mental disorders precipitated by various psychological and biological factors suggests that depression might be an expression of an inborn mild reaction pattern of the human brain. With progressing brain dysfunction more severe patterns like psychosis are expressed.

Key words schizophrenia and depression · early course · prodromal stage · Jacksonism · hierarchical reaction patterns of the brain

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Introduction

Recent long-term follow-up studies of schizophrenia, schizoaffective and affective disorder are consistent in reporting clear-cut overlap in episodes of these disorders. Focusing on unipolar depression, as we will for reasons of methodological and theoretical expediency, one comes to the conclusion that depression is a frequent comorbidity disorder of schizophrenia – the reverse, comorbidity of schizophrenia or at least of non-affective psychotic episodes in recurrent unipolar depression, is rare (Angst 1995; Crow 1995; Mundt 1995; Marneros et al. 1995). The prevalence of depression ranges from 6 % to 75 % in the course of schizophrenia in general (Siris and Bench 2003), from 65 % to 80 % in first psychotic episodes and psychotic relapses (Herz and Melville 1980; Biehl et al. 1986; Koreen et al. 1993; Dobmeier et al. 2000) and from 4 % to 20 % in psychosis-free intervals (Koreen et al. 1993; Siris and Bench 2003). The reasons for this enormous variance are among other things methodological in nature: 1) whether diagnoses, syndromes or single symptoms, 2) whether point-, period- or lifetime prevalence rates are being looked at and 3) the illness stage of schizophrenia studied. These methodological details have to be taken into account, if one intends to study associations between schizophrenia and depression.

Schizophrenia and unipolar depression share a symptom dimension – a depression factor (Liddle 1987a, b; Lenzenweger and Dworkin 1996; McGorry et al. 1998; van Os et al. 1999) – and some of their risk factors, such as genetic risk (Kendler et al. 1993, 1996; Maier et al. 1993, 2002), mild loss of brain volume (Jones et al. 1994; Elkis et al. 1995; Hirayasu et al. 1998; Weinberger 1999; Heckers et al. 2002) and presumably also pre-, peri- and early postnatal complications of brain development (Jones et al. 1994; Elkis et al. 1995; van Os et al. 2002).

Mild anomalies of social and emotional behaviour and of cognitive achievement in childhood and adolescence and neuroticism as a personality trait are precur-

sors of both disorders (Maier et al. 1994; van Os et al. 2002; Krabbendam et al. 2004). Most of these risk factors are more frequent or more severe in schizophrenia than in depression. In contrast, stressful life events precipitate illness onset more frequently in depression than in schizophrenia (Bebbington et al. 1993; Dohrenwend et al. 1995).

The overlap in risk factors, the fact that depressive symptoms contribute to the risk of psychosis in vulnerable subjects (Krabbendam et al. 2004; Verdoux & van Os 2002) and the frequent coincidence of these syndromes suggest that depression and schizophrenia might share some of their aetiology (Hirsch et al. 1989). We tested these associations in the early illness course when both symptom dimensions are uninfluenced by antidepressant or antipsychotic medication and at 6-month follow-up under treatment.

Study sample and design

We studied

- a representative sample of 130 first-admission patients with a broad diagnosis of schizophrenia (International Classification of Diseases – ICD-9: 295, 297, 298.3, 298.4) aged 12 to 59 years – a subsample of the ABC Schizophrenia study sample (N = 276) (Häfner et al. 1999b, 2002).
- 130 age- and sex-matched first-admission cases with a diagnosis of a depressive episode (ICD-10: F32, 33, 34.1, 43.2), 67 % of whom suffered from moderate or severe depression, and
- 130 likewise matched "healthy" controls from the population of the study area.

Most of the data presented here were collected cross-sectionally at first admission and retrospectively back to illness onset and premorbid individual development by the Interview for the Retrospective Assessment of the Onset of Schizophrenia – IRAOS – (Häfner et al. 1992, 1999a, 2003). Follow-up assessment was done six months after first admission using the PSE and the PSE-CATEGO algorithm.

Results

A total of 81% of the patients with schizophrenia and 79 % of those with depression were drug-naive. The duration of the early illness course from the appearance of the first symptom until first admission was 5.3 years in schizophrenia and 7.2 years in depression. Mean age at first admission was 30.6 years for patients with schizophrenia and 29.9 years for patients with depression.

At first admission the lifetime prevalence rates for attempted suicide were 18.5 % for patients with schizophrenia, 29.2 % for patients with depression and 10.8 % for healthy controls (Cochran's q test $p < 0.01$). At a frequency of nearly 30 %, attempted suicide was of substantial clinical relevance before first hospital admission in the depressed group.

A comparison of the prevalences and ranks of the ten most frequent initial symptoms of schizophrenia and depression at onset showed no significant difference in nine of the 13 symptoms (Table 1). That means that in both disorders a depressive core syndrome (consisting of depressive mood, loss of self-confidence etc.), negative symptoms and early indicators of functional impairment (e. g. difficulties of thinking and concentration) frequently occur at the early stages of the prodromal phase.

Next we analysed the period prevalences of the ten most frequent initial symptoms – comprising a total of 17 symptoms – from age at onset until age at first admission in the three groups. As the significant differences in all but two items – dissocial behaviour and oversensitivity – between the two patient groups and healthy controls in the two columns far right indicate, depressive illness and schizophrenia can already be clearly distinguished from health at this early stage (Table 2).

Table 1 Percentages of probands presenting initial symptoms in schizophrenia (Sz) and depression (Dep) – symptoms ranked 1 to 10 in either group

Symptom	Schizophrenia		Depression		Sz vs. Dep
	%	Rank	%	Rank	
Worrying	19.2	4	14.1	5	n. s.
Headaches, other aches and pains	10.3	–	13.2	8	n. s.
Nervousness, restlessness	21.9	2	6.2	–	***
Anxiety	23.2	1	15.4	4	o
Difficulties of thinking, concentration	17.1	5	16.5	3	n. s.
Depressed mood	20.6	3	34.9	1	*
Loss of self-confidence	11.9	8	14.0	6	n. s.
Social withdrawal, suspiciousness	11.6	9	13.3	7	n. s.
Disturbed appetite, sleep	15.0	6	21.9	2	n. s.
Loss of energy/slowness	13.5	7	8.5	5	n. s.
Loss of libido	4.1	–	8.5	5	n. s.
Oversensitivity	3.3	–	9.3	9	o
Other changes in affect (blunted)	11.1	10	0.8	–	***

McNemar test: *n. s.* not significant; o $p < 0.10$; * $p < 0.05$; *** $p < 0.001$; (Source: Häfner et al. 2005)

Table 2 Comparison of the period prevalences from onset to first admission of the ten most frequent symptoms in the early course of schizophrenia, depression and among healthy controls – the symptoms were assessed retrospectively at age of first admission; symptoms ranked 1 to 10 in any of the three groups

Symptom	Schizophrenia		Depression		Normal controls		Sz vs. Dep	Sz vs. NC	Dep vs. NC
	%	Rank	%	Rank	%	Rank			
Worrying	74.6	9	94.6	4	26.9	6.5	***	***	***
Headaches, other aches and pains	49.2	–	66.9	–	30.8	4	**	**	***
Nervousness, restlessness	88.3	3	81.5	10.5	27.7	5	n. s.	***	***
Anxiety	88.1	4	81.5	10.5	26.9	6.5	n. s.	***	***
Difficulties of thinking, concentration	93.8	1.5	96.9	3	20.8	–	n. s.	***	***
Depressed mood	84.9	5	100.0	1	46.9	1	***	***	***
Loss of self-confidence	68.3	10.5	89.2	7	35.7	3	***	***	***
Social withdrawal, suspiciousness	79.8	8	90.8	6	13.8	–	*	***	***
Disturbed appetite and/or sleep	93.8	1.5	98.5	2	43.4	2	n. s.	***	***
Loss of energy/slowness	82.5	6	93.8	5	15.4	–	**	***	***
Irritability	65.4	–	68.5	–	26.2	8	n. s.	***	***
Delusional mood	68.3	10.5	4.6	–	0.0	–	***	***	*
Delusional misinterpretations, delusions of reference	80.3	7	6.2	–	0.0	–	***	***	**
Oversensitivity	22.3	–	52.3	–	25.4	9	***	n. s.	***
Dissocial behaviour	15.3	–	14.6	–	22.3	10	n. s.	n. s.	n. s.
Reduced spare-time activities	63.5	–	89.1	8	15.5	–	***	***	***
Reducted interests/citizen role	33.9	–	87.7	9	3.8	–	***	***	***

McNemar test: n. s. = not significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Source: Häfner et al. 2005

A comparison of the period prevalence figures between schizophrenia and depression revealed that, again, showing some degree of stability after onset, six from a total of 13 items (nervousness/restlessness, anxiety, difficulties of concentration, disturbed appetite or sleep, irritability and dissocial behaviour) occurred at similar frequencies (Table 2). Most of the items significantly different in frequency showed high rates in both groups (e. g. depressed mood 100 % vs. 85 %, social withdrawal 91 % vs. 80 %, loss of energy 94 % vs. 83 %). The only exceptions were the two delusional symptoms highly specific to schizophrenia.

The following two figures illustrate changes in the early illness course. Fig. 1 illustrates the increase in the frequency of the ten most prevalent non-psychotic symptoms in schizophrenia and depression from onset to first admission. Despite the numerous significant differences in frequency the early symptoms of the two disorders do not differ much and their profiles are almost parallel at the end of the early course. The increase in the prevalence of this core symptom pattern, visible from the very beginning and accounted for by depressive and negative symptoms and signs of functional impairment, on average reflects slightly deteriorating illness at the prodromal stages of schizophrenia and depression.

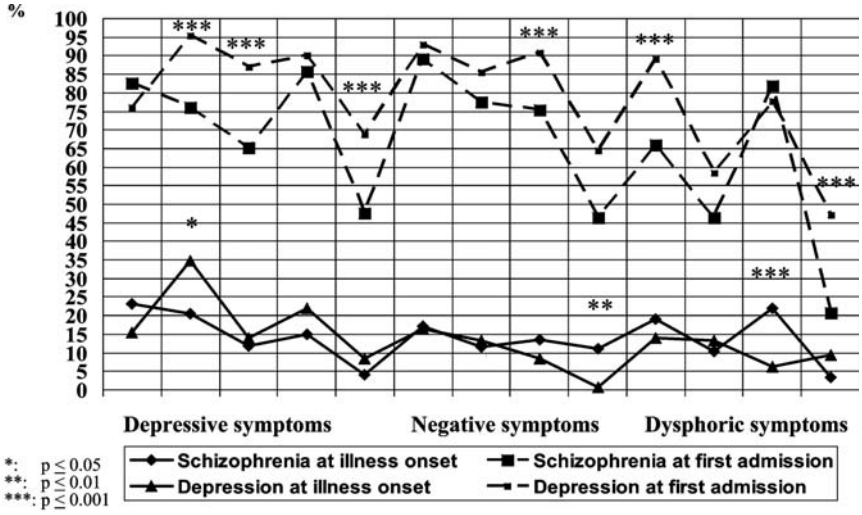


Fig. 1 The ten most frequent non-psychotic symptoms in schizophrenia and depression at illness onset and first admission (Source: Häfner et al. 2005)

Unlike non-psychotic core symptoms, positive symptoms increase considerably in the early course of schizophrenia, but not so in depression (Fig. 2), except the rare cases of psychotic depression, in which delusions and hallucinations do become slightly more frequent. Hence, it is the positive symptoms that distinguish the two disorders, though in most cases only at a later stage of the early illness course. Psychotic depression and schizoaffective psychosis seem to occupy an intermediate position.

Fig. 3 shows the sequence of symptom onset in the early illness course. Classified into five clinical categories, the symptoms of schizophrenia and depression are depicted by their first appearance in a time frame of 84 months preceding first admission. As expected, depressive symptoms appear first. As next negative symptoms and functional impairment as well as some dysphoric symptoms emerge, showing considerable overlap with depressive symptoms. In depression, the picture is very much the same, except for a still earlier onset of depressive symptoms.

Depressive symptoms reach a maximum in the psychotic episode (cf. Koreen et al. 1993; Siris and Bench 2003). As Fig. 4 shows, depressive symptom scores fall simultaneously with psychotic symptoms in the remitting first episode to low values in the interval. Relapse episodes seem to run a similar course, as demonstrated by Koreen et al. (1993) in a study of 70 first-admission cases of schizophrenia over 5 years first assessed every 2 weeks, later monthly. The 12-year follow-up of the ABC Schizophrenia Study sample, too, showed that depression was the most frequent symptom in a total of 333 psychotic relapses (an der Heiden et al., in preparation). The simultaneous course of psychosis and depression in

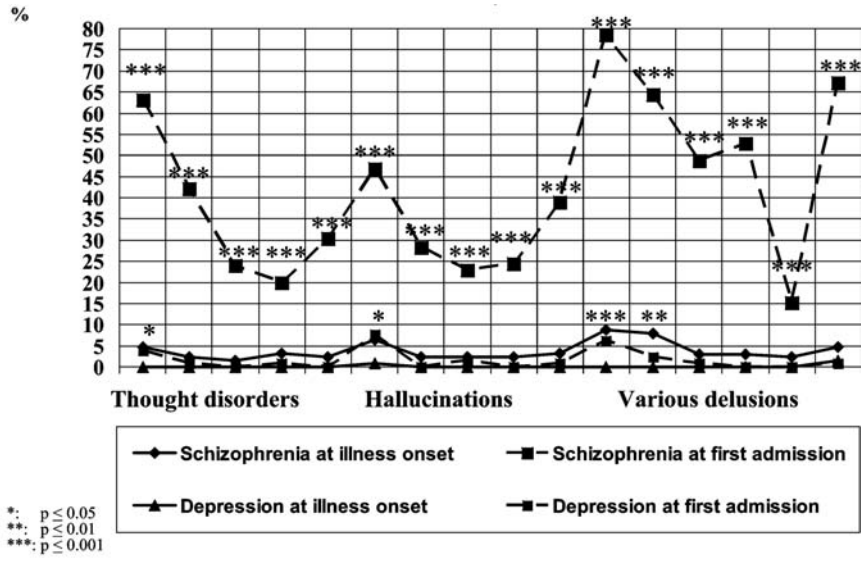


Fig. 2 Positive symptoms in schizophrenia and depression at illness onset and first admission (Source: Häfner et al. 2005)

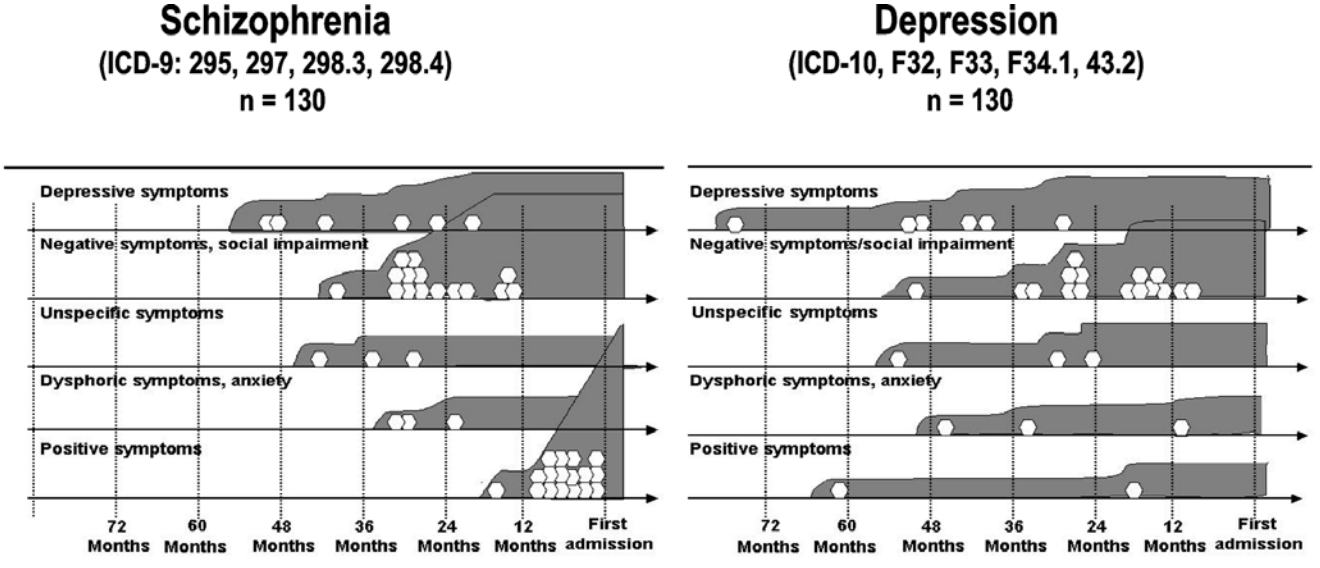
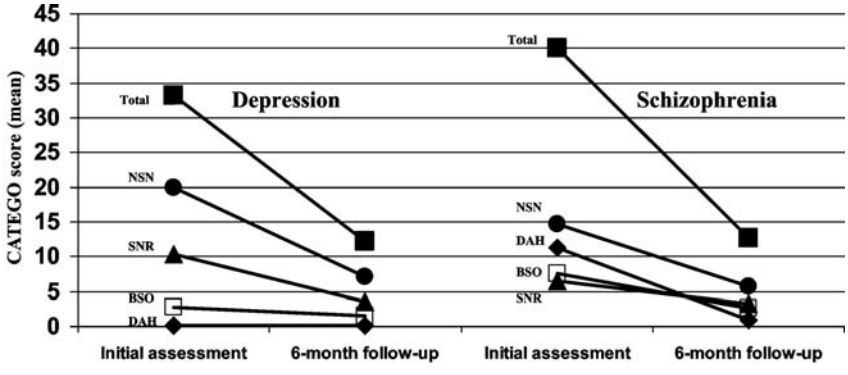


Fig. 3 Symptom onset (IRAOS) by five clinical categories before first admission (symptoms present in at least 5 % of the sample) (Source: Häfner et al. 2005)



Two-factor analysis of variance with repeated measurement factor

	Main effect Diagnostic group	Main effect Time	Interaction Time x Group
DAH	***	***	***
BSO	***	***	***
SNR	***	***	***
NSN	***	***	**
TOTAL	*	***	**

Comparison of diagnostic groups at initial assessment and follow-up (Wilcoxon)

	Initial assessment	6-month follow-up
DAH	***	*
BSO	***	**
SNR	***	n.s.
NSN	***	n.s.
Total	**	n.s.

n.s. = not significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Fig. 4 Mean CATEGO scores at initial assessment and 6-month follow-up in the depression and the schizophrenia group (Maurer et al. 2005)

the disease process suggests a causal association of the two syndromes.

It also becomes plain that schizophrenia and unipolar depression are very similar at their initial stages (Knights and Hirsch 1981; Koreen et al. 1993). It is not until psychotic symptoms appear towards the end of the early course of schizophrenia that the two disorders become clearly separable.

Discussion

In most cases the onset of both schizophrenia and severe depression is marked by a prodromal stage involving depressive and negative symptoms and growing impairment. It is fairly late in the early course that transition to a schizophrenic psychosis or, provided no psychotic symptoms occur, progression of depression or remission occurs. Even at the extremely short prodromal stages of acute and transient psychoses sleep disorders (50 %), depression and lack of drive (33 %) and anxiety (some 30 %) were the most frequent initial symptoms (Marneros and Pillmann 2004). Psychotic depressions – and presumably also depressive schizoaffective psychoses – seem to be located between the symptom dimensions of schizophrenia and depression. A diagnostic distinction between the two disorders at this early, prepsychotic prodromal stage and a disjunctive prediction of outcome in schizophrenic psychosis or a depressive episode does not seem possible. But the situation changes with the onset of the first psychotic symptoms. We hope that neuropsychological and/or neurobiological risk indicators will decisively improve the chances of discriminating between and predicting these disorders. With the onset of psychosis and the mounting psychotic episode the depressive syndrome, too, rather than remitting, gains momentum until the climax of the episode is reached, then remitting simultaneously with the psychotic episode (Fig. 5).

Underlying the depressive and the psychotic symp-

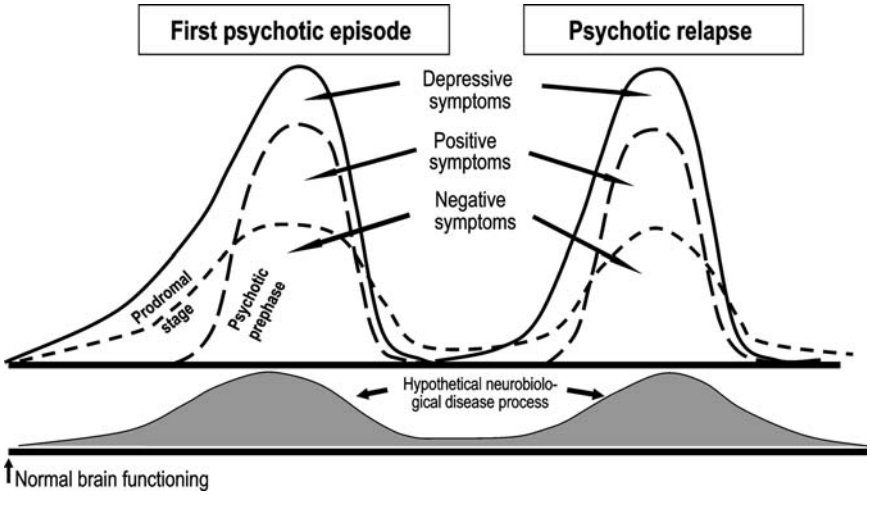


Fig. 5 Model of the sequence of the depressive (negative) and psychotic syndromes at the prodromal stage and in psychotic episodes of schizophrenia

tom patterns appear to be different types of central neurotransmitter dysfunctioning – e. g. noradrenergic and serotonergic in depression, dopaminergic and glutamatergic in schizophrenia – associated with different therapy responses. But many of the risk factors are common to both symptom dimensions, and most of them are clearly more frequent and more severe in schizophrenia, whereas psychogenic factors more frequently trigger depression. For this reason it seems reasonable to presume that depression occurring in the early course of schizophrenia and involving negative symptoms and increasing functional impairment represents an initial stage of the same disease process that in the further course leads to schizophrenic psychosis.

These results might turn out to fit into a more comprehensive, still speculative, model of the two disease dimensions called schizophrenia and unipolar depression. The depressive syndrome is the most frequent psychopathological disorder in most populations. It can be triggered by mild brain dysfunction caused by a great variety of factors, such as stress hormones, unfavourable life events, severe physical disease, schizophrenia and organic, especially incipient degenerative brain disorders.

Hence, the depressive syndrome seems to be a preformed reaction pattern of the brain associated with characteristic neurotransmitter dysfunctioning and originating in the genetic organization of the human brain. As the underlying brain dysfunction progresses, a further preformed reaction pattern, such as psychosis, will be expressed. Still further progression in cerebral dysfunction might bring forth organic syndromes and, later on, dementia.

Embracing these premises would mean – at least for depression and schizophrenia – that the model of separate disease entities, dementia praecox and affective psychosis (melancholia and manic-depressive psychosis) proposed by Kraepelin (1896) in his early works, is replaced by a hierarchical model based on a limited number of preformed reaction patterns dimensionally distributed by their severity, as put forward by Kraepelin (1920) in his later days: "Mental disorders are produced by various causes like the registers of an organ pulled by the organist. . . . Severe forms frequently activate milder ones."

This hypothesis modelled on the theory of hierarchical brain functions developed by Hughlings Jackson (1887) is supported by the assumption that in the course of evolution the human brain acquired new functions and neural networks on the basis of the existing ones. Therefore, it is reasonable to presume that a decreasing level of functioning caused by growing dysfunction is capable of triggering, either successively or simultaneously, a limited number of preformed patterns of response hierarchical in nature.

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