Dynamics of neural networks: a proposed mechanism to account for changes in clinical symptomatology through time in patients with psychotic diseases

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Summary  The classical Kraepeliane dichotomy between manic depressive insanity and the schizophrenias has been recently challenged from clinical and neurobiological quarters. It is not so infrequent to see patients shift from a manic to a schizophrenic symptomatology and vice versa. This paper proposes neurobiological mechanisms as to how these changes may occur, based on recent data on the functioning of neural networks at different modes.

INTRODUCTION

The Kraepeliane classification of major psychiatric diseases into manic depression and dementia praecox, later incorporated in the group of schizophrenias by Bleuler (1), has been taken almost as a bedrock assumption in psychiatry since its inception early in the 20th century by Kraepelin (2). While dissenting views have since been raised (3–7), mostly reflecting the difficulties in confirming clinically the proposed dichotomy, the notion is very much entrenched as revealed in the neo-Kraepeliane consensus expressed in the DSM IV (8), and in the view of a plethora of psychiatrists (e.g. 9).

Kraepelin was philosophically a convinced Platonist. He believed that the task of psychiatrists was to discover the essential diseases and their basic forms as expressed through the symptoms of patients. In Kraepelin’s own words, ‘Such, in their essential features, are the points of view from which the clinical forms of insanity may be grouped today’ (10). It is not surprising then that his proposed classification of mental diseases was basically an essentialist one.

In The Republic, in the doctrine of the psyche, Plato advances the notion of a tripartite composition of the psyche, an appetitive part, an emotional part and a rational part (11). (Later he incorporated the appetitive in the rational division.) He relegated the emotional part, the whole field of human affects, to a lower level. Emotions and rationality were considered independent parts of this platonic universe of ideas, thus unchangeable (11).

This philosophical stand was radically changed by Darwin’s theory. As Mayr (12) wrote, ‘None of Darwin’s new ideas was quite so revolutionary as the replacement of essentialism by population thinking.’ For essentialists, variation is the manifestation of imperfect reflections of the underlying constant essences. In contrast, population thinking acknowledges the variable groups as primary, and treats variation as intrinsic and fundamental. Hence, if variation is primary, we value diversity for its own sake.
Population thinking emphasizes the uniqueness of the individual and the critical role of individuality in evolution (13).

As presented in classical textbooks, the Kraepelalian dichotomy between affective psychosis and dementia praecox was and is basically Platonic, typological, as was Kraepelin’s ideology (14). However, today, no longer can we say wholeheartedly, as Jaspers did, that Kraepelin created ‘a common basis of psychiatric thinking.’

More than one study has failed to substantiate the presence of a bimodal distribution of the clinical features of manic depression and schizophrenia in patient populations (4,5). The breakdown of the essentialist or typological notions of emotion and cognition, and the understanding of their neurobiological basis, can help to explain the frequent clinical difficulty of identifying the two main diseases of the Kraepelinian dichotomy as categorically distinct.

Difficulties in reliably distinguishing between the two processes, manic depressive insanity and dementia praecox (schizo-phenia), were not foreign to Kraepelin himself. Thus in 1920 he wrote, ‘Perhaps it is also possible to tackle the difficulties which prevent us from distinguishing reliably between manic-depressive insanity and dementia praecox. No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. Nevertheless, it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect’ (cited in 5).

THE KRAEPELINEAN DICHOTOMY: A CRITICAL EVALUATION

It should not be surprising from Kraepelin’s own results that a significant number of studies show that the two major disorders emerging from his dichotomy present, in a large number of cases, significant overlap of lesion sites (15–22).

At present there is no consensus about the extent and reproducibility of abnormalities either at microscopic histopathological levels, e.g. abnormal neuronal migration in the entorhinal cortex (22), or at macroscopic levels, e.g. ventricular size (20). However, while not of universal occurrence, there are data substantiating overlaps of anatomic lesions in bipolar and schizophrenic conditions. Thus significant dilatation of the lateral ventricles, the ventricles to brain ratio (VBR), was observed in both schizophrenia and manic depression (19,20). In both groups of patients the mean values were significantly larger than the control group. Still to be answered is the question of the stability or progression of the enlargement. This is an issue which longitudinal studies are addressing, and which could throw some light on the problem of the developmental and/or degenerative character of bipolar and schizophrenic disorders (18).

Another significant cortical change is sulcal and fissure widening; both are seen with significantly higher frequency in schizophrenics and manic depressive patients than in control populations (15). Cerebellar atrophy and decreased brain volume also show higher incidence in these patients than in control populations (20).

Volume decrease on the left superior temporal gyrus has been reported in schizophrenics with auditory hallucinations (15) and on the right hemisphere in hallucinating bipolar patients (17). Also in the temporal lobe, enlargement of the temporal horn of the lateral cerebral ventricles has been described in both schizophrenic and bipolar disorders compared to a control group (17).

Similar pathomorphology, decreased volume of limbic (medial temporal) structures in schizophrenia (16,17) and bipolar disorders (15) is also in keeping with Kraepelin’s own view that the ‘formulation of the problem (manic depression and schizophrenia as essentially different illnesses) may be incorrect’ (cited in 5).

Moreover, studies on the evolution of neocortex cytoarchitectonics and myelization clearly show that many regions of lesion overlap correspond to archipallium structures that Barbas (23), Nauta (24), Yakovlev (25) and Sanides (26) showed to extend and be represented in the neopallium hence signalling the powerful association between emotion and cognitive activities of the brain (23,27,28).

Also as noted by Barbas (23), the main anatomical regions of lesion overlap, limbic structures and prefrontal limbic cortices, are endowed with special characteristics. Thus the widespread connectivity of these zones in adulthood is parallel to the one most other neural systems show, but restricted only to their development periods. Some molecular markers (e.g. DARPP 32 phospho-protein and GAP 43) also broadly distributed during development became preferentially located in limbic structures in mature animals. While the retention of developmental features may account for some of the remarkable plastic properties of limbic regions, they could also underlie the selective vulnerability of the same zones to chemical or physical trauma (23). Hence the hypothesis that both schizophrenia and manic depressive psychoses could be considered as developmental diseases (reviews in 18).

In 1971, Sheldrick et al. (29) pointed out a subset of patient population who present with clearly defined schizophrenia but who later develop episodes of illness which were characteristically affective in form. In turn, the converse picture, typical affective illness presentation leading to process schizophrenia was also documented by them. Moreover, the fact that there may be a general
psychosis factor that cuts across psychotic diagnosis was also brought up by Harrow et al. (30) in an investigation on thought pathology in manic and schizophrenic patients. The results of Harrow et al. revealed, firstly, that thought disorder is not unique to schizophrenia, being observed frequently in manic states too and, secondly, that some factors involved in manic and schizophrenic thought pathology are similar. Of note within this context was also the fact that vulnerability for the two disorders, schizophrenia and manic depression, was not fixed in a rigid way from the genetic standpoint.

The intriguing clinical (3,5–7), anatomical (17,19,21) and pharmacological (32) overlaps between affective and schizophrenic psychoses, led Freedman (33) to propose that there may be a 'general biology of psychosis that would cut across traditional lines'. In fact, the hypothesis of a continuum of psychosis, a development of the concept of the 'unitary psychosis' of the 19th century is again seriously considered (see e.g. 7).

For the German psychiatrist Wilhelm Griesinger, one of the proponents of 'unitary psychosis' in the 19th century, there was no such a thing as mental diseases, but only brain diseases (34).

Recently, the late Prof. Lehmann suggested an alternative to the problem of classification of psychotic disorders. Prof. Lehmann argued that 'Griesinger's idea of unitary psychosis becomes more plausible if we, in contrast to him, consider psychosis as an autonomous psychiatric entity, category, dimension or axis that may or may not accompany other psychiatric diagnoses. Twenty to thirty percent of affective disorders are also psychotic, if psychosis is strictly defined as a condition with disturbed reality testing as manifested by one or more of three symptoms: hallucinations, delusions and severe formal thought disorder, the so-called positive symptoms of schizophrenia. The latter disorder is in more than 90% psychotic. However, there is also schizophrenia with only negative symptoms, that is without psychosis. Such cases may now be diagnosed as severe schizotypal personality disorder, as latent schizophrenia, or as simple schizophrenia, a diagnosis reintroduced into DSM IV'.

'A new, autonomous, diagnostic category of psychosis might be developed which would be independent of other psychiatric disorders. It would be a unitary psychosis, a condition that may be co-morbid with many other psychiatric disorders. Unitary psychosis might have its own biological substrate…. It is also conceivable that psychosis might be viewed as a principal dimension with manic-depressive, schizophrenic, confusional or other subtypes in which overlap and crossover of subtypes is not excluded' (35).

Tim Crow has recently proposed similar ideas in his theory of a unitary psychosis as a retroviral disease with a genetic background. He views schizophrenia and affective disorders as being on a continuum (36).

**SYMPTOM FORMATION: NEUROPHYSIOLOGY**

How can some of these peculiar clinical characteristics be interpreted from current knowledge of fundamental neuroscience? How can nervous systems generate from similar loci, different symptomatologies in time? To get some understanding of this problem we should examine some current ideas on the organization and function of neural networks.

Neural networks depend upon interactions among multiple nonlinear processes at the cellular, synaptic and network levels themselves. While the notion that the functional organization within a network is under dynamic control has been already stated by Sherrington, new evidence has revealed the all-encompassing generality of this fact.

The working out of a particular network (i.e. knowledge of the connectivity of a network alone) is not sufficient to predict its behavior(s) (37). This is due to the fact that the task performed by a specific network depends upon what influences its components (network, synaptic and cellular) are being subjected to at the time. Physical (e.g. field effects), chemical (e.g. hormones) or environmental (e.g. social milieu) factors can throw the performance of an anatomical network into any one of several modes depending upon the particular combination of ongoing processes (37–39). By mode is meant the manner in which a network processes signals or generates an output pattern, thus each mode represents the functional organization of the network that gives rise to a function or task. Transition between modes is determined by the nature of afferent inputs or changes in the chemical, physical or social milieu that alter the properties of the elementary components of the network. Networks can be multifunctional.

To wit, afferent input to some neural networks may serve not only to activate, but also to configure them into one of several functional circuits. Thus, e.g. in the sea slug* Tritonia*, the same neural network may mediate escape withdrawal or escape swimming, depending upon the pattern of activation that it receives; and such networks have been named polymorphic (37) (see Fig. 1). An added factor to the array of functional possibilities of a specified network is revealed by studies that indicate that a given neuron, or even a given axon, probably conveys information at the same time in two or more distinct codes for different recipient cells or arrays. This high level of plasticity is manifested by all nervous systems, in particular the human one (40–47). For example, it has been shown that the direction of the vestibulo-ocular reflexes can be reversed when the direction of visual images is inverted.
by the use of prisms. Thus nervous systems are endowed with the capacity to change what were considered ‘hard wired’ reflexes such as the vestibulo-ocular and even spinal ones.

**DYNAMICS OF NEURAL CIRCUIT OPERATION: IMPLICATIONS FOR PHYSIOPATHOLOGY**

Can these data from experimental neurophysiology lead to any hypothesis of heuristic value regarding mental diseases, and, in particular, patients that present with alternative symptomatology of schizophrenia and bipolar diseases plus overlapping lesion sites.

From the outset it is fundamental to recognize the importance of polymorphic networks (37) and the influence of modulatory inputs (39) to understand neural function during normal and pathological conditions. Mountcastle clearly stated, ‘The properties of microcircuit operations are emergent, for they can not be predicted from what is known of the action of single neurons. These network properties are likely to be highly dynamic, changing markedly and rapidly under the influence of modulatory inputs’ (48).

These phenomena can provide a measure of explanation to account for the overlap of lesion sites in the CNS observed in cases of manic depression and schizophrenia as noted, and of symptom alteration in time (49). They can also underlie mechanism(s) for the well-established fact that a qualitative neurophysiological abnormality is not necessarily associated with a unique symptom complex (50).

It is conceivable that patients could manifest different symptomatology in time if similar neuronal networks involved in the generation of these symptoms are set in different modes under the influence of different modulatory inputs at different times.

Pathological modulation, e.g. hormonal imbalances, of these underlying processes can lead to pathological conditions. A representative example of how this type of reasoning can potentially enhance understanding of mental disease is exemplified by a series of studies carried out toward the elucidation of the physiopathology of some symptoms in a subset of depressive patients and its subsequent therapeutic implications.

The research stemmed from a triad of relations:

1. A sizable, > 50%, group of depressive patients present with high levels of circulating cortisol and non-suppression on the Dexamethasone Suppression Test. The incidence of depression during Cushing’s syndrome is very high (51,52). Frequently the depression is alleviated by therapy of the endocrine condition and not by psychodrugs, tricyclic antidepressants (53).

2. The hippocampus is a primary target for corticoadrenal steroids (54), and also the brain region from where long-term potentiation, a putative memory mechanism, is more easily elicited (55). Glucocorticoid (GC) in large doses produces a decrement of long-term potentiation (LTP), a memory related process (54).

3. Many psychological processes affected during both depression and Cushing’s syndrome are ones in which the hippocampus plays an important role, e.g. memory, attention, anticipatory anxiety, space memory (54–57).

To understand how a network operates, the flow of activity within the network must be described quantitatively. One method for quantification is to define states of activity within the network. A state is defined as the spatial distribution of activity within the net. Anatomical connectivity refers to the pattern of monosynaptic connections among a group of neurons. Functional connectivity, in turn, concerns the effect of one cell upon another by whatever pathways, mono or polysynaptic, interconnect

![Diagram](http://www.AnnualReviews.org/)

**Fig. 1 A.** Network diagram showing the monosynaptic connectivity between interneurons of the *Tritonia* escape swim system. **B.** Network configuration reflecting the functional connectivity when C2 is silent. In this configuration (mode), the network contributes to reflexive withdrawals. **C.** Network configuration when C2 is active. In this mode the network generates an alternating burst pattern between DSI and VSI which in turn activates moto-neurons for each flexion movement. Pathways with more than one symbol indicate multi component synapses.

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the two cells. Anatomical connectivity defines the constraints of a network but functional connectivity determines the activity pattern (37,39).

As already mentioned, the hippocampal structure, a main component of the limbic system, plays a significant role both in affective as well as cognitive activities. It is, therefore, of interest that size and structural abnormalities have been reported in this structure in the two main categories of the Kraepelinean classification, schizophrenia and manic depressive psychosis.

We hypothesized that a multifunctional network like the hippocampus can, under the effects of different modulators, behave in different modes. In turn, different modes of operation can give rise to different symptoms, e.g. psychotic ones such as delusions and hallucinations in one mode and severe mood disturbances and memory deficits as in depression in another mode (54–57).

Activation of the monosynaptic pathway that from the entorhinal cortex goes to the dentate gyrus (DG) can be modulated via the cholinergic septohippocampal path that disinhibits granule cells by reducing GABA output from interneurons (58,59). Thus, blocking this disinhibition from the interneurons (through atropine-like compounds) will significantly affect DG output.

The fact that high doses of atropine-like compounds lead to restlessness, irritability and hallucinations or delirium are well established (see 60). By increasing and/or decreasing neural excitability and affecting long-term processes in hippocampal zones, unbalanced steroid secretion can set an abnormal mode in those networks giving rise to symptomatology of affective diseases (54–57).

**CLINICAL CONSEQUENCES OF NEURAL CIRCUIT DISRUPTION**

Chronicity of stress system activation can lead to the maintenance of conditions such as adult melancholic depression (61). In these circumstances, adrenal cortical secretion shifts towards the glucocorticoids and a reduction of C19 steroids such as androsterone sulfate (61,62).

We have argued, based on experimental studies on the effects of steroid hormones and their reduced metabolites on long-term potentiation and on clinical studies (54–57), that some of these endocrine effects on nervous systems can underlie a measure of depression symptomatology, memory disturbances, feelings of space confinement, and low mood in both Cushing’s and depressive patients.

In 1990, at a CIBA Foundation Symposium on Steroids and CNS Activity we proposed partial control of adreno-cortical secretion (partial suppression) as a therapy adjuvant in unremittant depressive diseases. Clearly this is a medically risky and delicate procedure (55). Price et al. have recently reviewed later trials and summarized results with this method (63). In order to avoid the dangerous reduction of adrenocortical secretion produced by indiscriminate suppression with these drugs (Ketoconazole, metyrapone, aminogluthethimide), we thought that a more rational approach would be to identify hormones which can counteract each other in their CNS effects. We have been investigating various hormones in search of these counteractive effects (54,64–66).

The feasibility of using long-term changes in activity (LTP and kindling) in the hippocampal network and its pharmacological modulation by steroid hormones or other compounds (e.g. cocaine) as a preclinical model to study depression disorders has also been suggested by Post et al. (67).

In related to the effects of hormonal modulators related to depression, we investigated the interaction of corticosterone, the main rat GC, and the neurosteroid dehydroepiandrosterone sulfate (DHEAS) on LTP in the rat dentate gyrus. Previously we reported that corticosterone had decremental effects (55) while DHEAS enhanced LTP (68). However, as predicted (66), simultaneous injection of corticosterone and DHEAS elicited EPSPs and population spikes that were not significantly different from those observed in control animals (69). We recently showed that androsterone sulfate also enhanced LTP in rats, dentate gyrus (70).

These results indicate then that DHEAS can counteract the decremental effects of corticosterone on hippocampal LTP. Based on these data we asked, could DHEAS antagonize the putative depressogenic effects of elevated cortisol in patients? On theoretical grounds we proposed that DHEAS could be used in the treatment of depression (66).

Subsequent clinical data upheld this prediction from this experimental and theoretical work (71,72). DHEAS has been shown to be an efficacious new natural hormone in the treatment of depression. Thus a combined clinical, animal experimental and theoretical work on the hormonal effects in a phenomenon (LTP) on the hippocampal network led to the proposal of a successful new treatment for depression.

The reviewed work supports the notion that a valid strategy to explore the neurobiological underpinning of mental diseases is to identify neural networks involved in the expression of a specific behavior (memory, attention) and study compounds (preferentially natural, hormones, neurotransmitters) that modulate their activity.

It is conceivable that the operation of these neural circuits at different modes, determined in turn by the influence of different endogenous or exogenous substances, may underlie abnormal aspects of behavior responsible for pathological symptoms in mental diseases, e.g. attention deficits in schizophrenia (73,74), and memory alterations in depression (56,75).
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