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Is 'bipolar disorder' the brain's autopoietic response to schizophrenia?

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SUMMARY

Evidence is accumulating that schizophrenia and bipolar disorder are related conditions. This paper proposes a particular form of relatedness. If 'schizophrenia' is a mind/brain 'trapped' between waking and dreaming, in a disordered in-between state, then bipolar 'disorder' could actually be an attempt to restore order.

The mind/brain is a self-producing, self-organizing system. Autopoiesis applies to such systems. Neuromodulation accomplishes self-organization in the mind/brain. If schizophrenia is a state in-between waking and dreaming, characterized by aminergic/cholinergic interpenetration and dopaminergic imbalance then bipolar 'disorder' could be a modulatory response. This autopoietic reaction may take the form of either aminergic hyperactivity aimed at producing a purer waking state, (precipitating mania in the waking state), or cholinergic hyperactivity aimed at producing a purer dreaming state, (producing depression in the waking state), or both, resulting in rapid cycling bipolar disorder. Thus bipolar activity may be an autopoietic response aimed at restoring differentiation to the in-between state of schizophrenia.

Introduction

Modern psychiatric practice continues to recognize and diagnose two major psychoses: schizophrenia and bipolar disorder. There is current academic debate, however, on whether they are indeed distinct. In the face of increasing evidence that they share the same aetiology [1–4], exhibit symptomatic overlap [5–7], can follow a similar deteriorating course [8,9], involve sleep disturbances [10,11] and can be difficult to distinguish clinically [1,12,13], it appears they may be related. This paper suggests a particular form of relatedness. If schizophrenia is a disordered mind/brain state 'trapped' between waking and dreaming [14], then bipolar 'disorder' may actually be an attempt to *restore order* – the mind/brain's autopoietic reaction. This does not deny that bipolar disorder, as a response to schizophrenia, frequently gives rise to problems of its own.

The hypothesis is: 'Bipolar disorder' is an autopoietic response to schizophrenia.

The concept of 'autopoiesis' captures the idea of holistic self-producing systems [15,16]. I am such a system. I produce myself as a unitary being, a bounded entity. Self-producing systems are also self-organizing ones, '...an autopoietic system has a domain in which it can compensate for perturbations through the realization of its autopoiesis, and in this domain it remains a unity' [15]. So autopoietic systems can organize to reconstitute themselves – such organizing potential is inherent in the production of a coherent whole from constituent parts. The brain is an self-organizing system [17]; if the brain is disordered it will attempt to regain wholeness through the realization of its own autopoiesis.

Holistic organization occurs in complex interactive systems. Such systems are subject to chaos theory. The brain is an instance, indeed the most striking known example, of a complex interactive system. Chaos theory indicates that one feature of such systems is that they are attracted to [18] and operate most creatively on 'the edge of chaos'.

> *'For complex non-linear dynamic systems with rich networks of interacting elements, there is an attractor that lies between a region of chaotic behaviour and one that is 'frozen' in the ordered regime, with little spontaneous activity. Then any such system, be it a developing organism, a brain, an insect colony, or an ecosystem will tend to settle dynamically at the edge of chaos. If it moves too far into the chaotic regime it will come out again of its own accord; and if it strays too far into the ordered regime it will tend to 'melt' back into dynamic fluidity where there is a rich but labile order, one that is inherently unstable and open to change'* [19].

In the context of the hypothesized relationship between schizophrenia and bipolar 'disorder' the key phrase in the above quotation is *'If it* [the brain] *moves too far into the chaotic regime it will come out again of its own accord...'*. Schizophrenia is undoubtedly a dysfunctional 'chaotic' brain state. In such a state of disorder, would the brain attempt to come out of its own accord-to reconsitute itself? Autopoiesis indicates that it would. Chaos theory also confirms the likelihood of an autopoietic response

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inherent within the dynamism of all complex interactive systems – if and when they 'stray' too far 'over the edge'. From the perspective of autopoiesis and chaos theory, this paper argues that bipolar 'disorder' is the autopoietic reaction to schizophrenia. How is it expressed?

Hyper-aminergic and cholinergic activity?

If schizophrenia is a mind/brain 'trapped' between waking and dreaming – in a 'mixed' state between the two – then an autopoietic response would attempt to 'break out' of this 'trap'. Any such self-organizing response occurs though the brain's modulatory systems [17].

Waking and dreaming/sleeping are constituted as dissimilar through the action of neuromodulators. During waking the brain/mind is 'running on' aminergic neuromodulators; while sleeping and dreaming the brain/mind is modulated by the cholinergic system [20,21]. Dopaminergic neuromodulators are present in both waking and dreaming [20–23], although mesolimbic systems may predominate during dreaming and mesocortical during waking. Due to dopaminergic activity, both waking and dreaming states are characterized by activation and arousal [22,23]. So rather than thinking of dreaming as being embedded in (and inherently linked to) sleeping it may be better to conceptualize sleep as a 'door' that can open into one or other of two 'rooms'. These 'rooms' are activated brain states-waking consciousness and dreaming consciousness.

The aminergic and cholinergic sets of neurotransmitters are classed as neuromodulators because they can produce *global* changes in brain states [20,24]. Most notably they produce the remarkable brain change that turns dreaming into waking (and waking into sleeping). The distinction between these two sets of neuromodulators is not absolute. Hence, whilst the experiences of being awake and dreaming are, in many ways, poles apart they are not totally different in kind. Moreover, waking and dreaming are not always totally differentiated. Whilst going to sleep and waking up the mind/brain is in a transitional aminergic/cholinergic zone. During dreaming 'lucidity', there is awareness of the dreaming state and, sometimes an ability to direct the dream plot. During waking 'day-dreaming' is possible, attention and concentration drift as the mind becomes preoccupied with internal precepts. Potentially, the mind/brain could occupy any point within a waking/dreaming multidimensional space [25]. But waking and dreaming states of mind are usually differentiated – normal functioning depends upon this.

If the mind/brain was in a de-differentiated state, in-between dreaming and waking, the aminergic and cholinergic systems would be interpenetrated and dominergic systems (present during waking and dreaming) would also be disrupted. If schizophrenia is a mixed state, during schizophrenic waking cholinergic neuromodulation would be higher than normal, with the aminergic lower and visa versa in dreaming. The mesolimbic dopaminergic activity that drives dreaming would be partially projected into waking, with mesocortical dopaminergic function during waking partially present during dreaming. Also the W/REM/NREM cycle would be disrupted. Autopoiesis would attempt to regenerate normal functioning through restoring differentiation.

There are several ways this could happen. First, attempts to produce a purer waking state through aminergic hyperactivity; such attempts could result in mania in the waking state, sleep disturbances and suppression of REM dreaming. Second, efforts to produce a purer dreaming state through cholinergic hyperactivity, this could precipitate depression in the waking state, an increase in REM dreaming, shorter REM latency, induced REM frequency and either over-sleeping due to cholinergic hyperactivity or sleep loss if the increase in REM displaces NREM. Third, both aminergic and cholinergic hyperactivity could alternate, resulting in rapid cycling bipolar 'disorder'. Is the literature suggestive of this?

'Imbalance' theories of psychosis

Many 'imbalance' or 'interaction' theories of psychosis have been proposed. A cholinergic–adrenergic imbalance theory of mania and depression has been suggested [26,27]. Cholinergic reversal of manic symptoms has been demonstrated [28]. Schizophrenia (as observed in the waking state) and dreaming are both characterized by serotonergic and noradrenergic demodulation and cholinergic hypermodulation [29–32]. Noradrenergic instability has been suggested in schizophrenia [33]. Cholinergic–dopaminergic interaction effects have been implicated in the expression of the positive and negative syndromes in schizophrenia [34]. Specifically, an anti-cholinergic agent administered to schizophrenic patients produced a significant increase in positive symptoms and a decrease in negative ones; the hypothesis being that the anti-cholinergic agent inhibited the containing effect of hypercholinergic activity on the dopaminergic-induced positive symptoms, whereas the anti-cholinergic improved the negative ones [34]. Moreover, the 'excess' dopamine (DA) hypothesis of schizophrenia has been superseded by an 'imbalance' one; which suggests that mesolimbic subcortical DA hyperactivity precipitates positive symptomatology whereas hypoactivity in mesocortical DA projections to the prefrontal cortex is associated with negative symptomology [35]. Any deficit in mesocortical DA activity may disinhibit mesolimbic DA function; a dynamic relationship between these two DA projections has been proposed [35,36] It has also been suggested that, 'an abnormally reactive cortical cholinergic input system represents a necessary correlate of a sensitized mesolimbic dopaminergic system. . .' [31]. Moreover, dysfunctions in both the serotoninergic and dopaminergic systems have been proposed in schizophrenia, with the serotoninergic mediating negative symptomatology and dopamergic precipitating the positive symptoms [37].

There are also indicative findings on the relationships between schizophrenia, bipolar 'disorder' and disruption to the W/REM/NREM cycle. Both schizophrenia and bipolar disorder are associated with sleep disruption [10,11]. Short REM latency is also a well accepted marker for clinical depression [38]. Pharmacological and neurophysiological findings demonstrate that cholinergic neuromodulation induces REM and depression, whereas aminergic neuromodulation delays REM and suppresses both REM and depression [39,40]. Such data is consistent with aminergic–cholinergic imbalance [18,19,41]. Acutely ill schizophrenics do not develop REM pressure following sleep deprivation [42] an indication that the W/REM/NREM cycle is dysfunctional. Similarities between the symptomatic profile of narcolepsy and schizophrenia have been noted [43]. This finding is indicative of cholinergic hyperactivity in both conditions, moreover, narcolepsy responds to anti-cholinergic antipsychotics [44].

In sum, this body of research portrays complex *dynamic* (rather than static) imbalances between cholinergic, serontonergic, noradrenergic and dopaminergic systems and dynamic disruption to the W/REM/NREM cycle in schizophrenia; it is also suggestive of complex restorative activity to regain 'balance'. If 'imbalance' became so severe that the aminergic and cholinergic systems were interpenetrated then restorative activity to reverse this state would become very difficult. What could produce such severe difficulties? The membrane theory of schizophrenia [45] may explain this.

The 'membrane' theory of psychosis

Neurons are surrounded by plasma membranes which regulate activities such as '...impulse conduction, neurotransmitter release and uptake, and neurotransmitter activity at both pre- and post-synaptic sites' [45]. Membrane functionality is also essential for reuptake of excess neurotransmitter after binding on the post-synaptic site [46]. It would, therefore, be anticipated that disruption to the structure of neuronal membranes would lead to serious malfunction in all neurotransmitter systems [45,47]. The composition of neuronal membranes is highly dependent upon essential fatty acids [45,48].

There are essential fatty acid (EFA) abnormalities in the neuronal cell membranes of individuals with schizophrenia [45,49–53] and bipolar disorder [54,55]. Several double-blind, placebo-controlled trials have demonstrated the efficacy of a particular omega-3 EFA, eicosapentaenoic acid (EPA), as an adjunct treatment for already medicated patients with schizophrenia [56–59] or bipolar disorder [60,61]. EPA may accelerate treatment response in patients with first-episode psychosis [62] and delay or prevent the onset of psychosis [63]. There are also indicative findings that EPA benefits drug-naïve individuals with schizophrenia [64,65]. As argued in the previous section, for some time schizophrenia was thought be linked to dysfunction of the dopaminergic system alone but it is now believed that other neurotransmitter systems are also involved: serotoninergic; cholinergic; and noradrenergic. Such expansion in the neurotransmitters thought to play a role in schizophrenia lends additional weight to the membrane hypothesis – as membrane abnormalities would disrupt all neurotransmitter systems [45].

Disruption to all neurotransmitter systems may erode the differentiation between the dreaming and waking states eventually resulting in the two becoming chaotically and chronically interpenetrated or 'mixed up' – a state currently labelled as 'schizophrenia'. But, as argued above, schizophrenia is an inherently dynamic condition, as such it may trigger an autopoietic response. Aminergic surges attempt to achieve a purer waking state; similarly cholinergic ones try to attain a purer dreaming one. This implies that schizophrenia and bipolar disorder share the same aetiology, being essentially the same condition. They are expressed differently because bipolar disorder represents an autopoietic response. Why did the two conditions come to be understood as different?

The Kraepelin dichotomy

Emil Kraepelin is seen as the founder of modern scientific psychiatry. In accordance with one of the central tenets of science he believed it imperative to *classify* psychiatric disorders. His thinking was that even if illnesses shared one or more symptoms, in order to classify clinicians should pay attention to the general profile of the disease. Classification is a form of theorizing. Classification both builds on a particular understanding and directs future thinking about the phenomenon in question. Once a previously unstructured area of interest is classified, for instance, into two distinct domains future research will tend to bifurcate. If the original classification was misguided, research is impeded as attention becomes focussed on the analysis of difference rather than a synthesis of findings.

Kraepelin was responsible for the differentiation of bipolar disorder from schizophrenia, conditions that had previously been subsumed within generalised insanity [66]. He classified two conditions: dementia praecox and manic–depressive illness [67]. This differentiation reflected Kraepelin's perceptions on the general profile of the two conditions, he saw dementia praecox as a dementing, deteriorating condition whereas he identified manic–depressive illness as exhibiting a cyclical course with recovery between episodes [12]. Bleuler criticised the label 'dementia praecox' judging that this form of madness did not follow a 'dementing' pathway, he substituted the term 'schizophrenia' [68]. More recently, the term 'bipolar disorder' replaced 'manic–depression' as it was seen to be less stereotyping.

Kraepelin came to question his own dichotomy [12,69] nevertheless, it became enshrined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* and WHO's *International Classification of Diseases* [12]. Moreover, when Kasanin introduced the term 'schizoaffective disorder' [70], he intended to highlight the similarities between bipolar disorder and schizophrenia and erode the Kraepelin differentiation [7]. Indeed, although the general direction of Kraepelin's thinking was to classify through differentiation, in one respect he followed prior opinion on relatedness, taking mania and depression to be aspects of the same disorder, indeed he coined the term 'manic–depression' [71].

Kraepelin believed that psychiatric disorders stemmed from genetic inheritance and/or bodily dysfunction. He was, therefore, opposed to the ideas of Freud who thought that psychosis was precipitated by psychological factors, most commonly as the result of traumatic episodes in early childhood. Although Freud's ideas on aetiology were dominant during the first half of the 20th century, the psychiatric profession has now, largely, returned to the notion of a genetic and/or organic causal pathway for psychosis. However, throughout the intellectual upheaval on 'causes', psychiatrists remained wedded to the idea that there were several *distinct* psychiatric illnesses, indeed new ones were added during the 20th century, personality disorder, for example.

Yet, as pointed out earlier, many are now sceptical about the separate categorization of bipolar disorder and schizophrenia, some conclude that we are at the beginning of the end for the Kraepelinian dichotomy [1]. Indeed, distinctions between many psychiatric illnesses are fuzzy [66], and symptomatic profiles overlap considerably, 'The recent findings are compatible with a model of functional psychosis in which... [there is] susceptibility to a spectrum of clinical phenotypes... [or indeed]... a multidimensional space [where] in addition to bipolar disorder and schizophrenia there is genetic overlap between the functional psychoses and major depressive disorder – and, indeed, other disorders – with extension into sub-clinical (or normal) variation' [1]. Some are critical of the idea of 'spectrum', asserting that '...schizophrenia is in fact a reified umbrella concept constructed by psychiatry to cover a heterogeneous group of disorders' [72]. How is the heterogeneity in schizophrenia expressed? It has been argues that, 'Heterogeneity in clinical presentation and course is routinely observed, and heterogeneity of disease processes is likely' [73].

Although many now argue that schizophrenia and bipolar disorder are related, the diagnosis of bipolar disorder can be uncontroversial, 'Classic bipolar patients are so different from normals and patients with other medical conditions and they demonstrate such a large variance in their thoughts and behaviour between episodes of mania and depression, that selection confidence is high [7]. Although, it appears that even classic bipolar disorder can regress to schizophrenia. In a recent comment in *The Lancet* a clinician reflects, 'My clinical experience over many years indicates, in many instances, a temporal progression along this continuum from symptomatically classic bipolar disorder to schizophrenia with the reverse being uncommon' [13].

In sum, the picture is of increasing evidence that the major psychoses share a common aetiology, are related, indeed, that there is a spectrum of overlapping functional psychiatric disorders that shades into normal variation. On the other hand, there are arguments that 'schizophrenia' has no unique symptomatic profile, that it is an umbrella concept covering a range of heterogeneous

disorders. Could both, seemingly paradoxical, ideas be correct? Could functional psychiatric disorders be both *related* in terms of aetiology and *heterogeneous* with regard to expression?

Discussion: can bipolar 'disorder' restore order in 'schizophrenia'?

If schizophrenia results from the chaotic and chronic interpenetration of the waking and dreaming states, the paradox between common aetiology and heterogeneous expression is explained. Common aetiology equates to genetic profiles expressed as neuronal cell membrane abnormalities that differentially disrupt all neurotransmitter action. Dynamic imbalances between cholinergic, serontonergic, noradrenergic and dopaminergic systems and disturbances in the W/REM/NREM cycle result. Over time the aminergic and cholinergic neuromodulators could become interpenetrated.

Heterogeneous expression is a consequence of the complexity of the neurotransmitters involved. There is a diverse and complex possibility space for aminergic/cholinergic interpenetration. The various 'imbalance' theories of schizophrenia, outlined above, may all have some purchase as the expression of 'schizophrenia' would take diverse forms dependent upon the extent of the involvement of the dopaminergic, serotoninergic, noradrenergic and cholinergic systems. Also different degrees of 'overlap' between the aminergic and cholinergic systems may exist. Such conclusions are in line with chaos theory which indicates that small changes (in this case, abnormality in cell membranes) lead to unpredictable (on the basis of initial conditions) large changes in the system (in this case, the ways in which and the degree to which the noradrenergic, serotonergic, dopaminergic and cholinergic neurotransmitter systems become interpenetrated). 'Disorder' results from the chronic interpenetration of the aminergic and cholinergic neuromodulators. However, some limited interpenetration of these systems may produce a creative 'edge of chaos' state. Indeed, chaos theory may indicate that complete differentiation between the aminergic and cholinergic neuromodulators may result in rigid brain order and a consequent loss of functionality.

The differential presence of positive and negative symptoms in schizophrenia can also be explained by disrupted aminergic/cholinergic interaction. Normal waking and dreaming are at the opposite ends of an aminergic/cholinergic continuum [25]. Cholinergic hypermodulation and aminergic demodulation during waking could precipitate what is termed the positive syndrome (*inter alia*, disordered thinking, hallucinations, delusions due to loose associations between ideas and the attribution of unusual significance to ordinary events) but may also explain some aspects of the negative syndrome (i.e. diminished social engagement). Whereas aminergic modulation and cholinergic demodulation during dreaming could give rise to aspects of the negative syndrome (*inter alia* gradual memory deficits due to the erosion of meaningful memory consolidation and organization, loss of identity, diminished interest in concerns and projects and the loss of a continuous sense of self). Moreover, as discussed earlier, increased cholinergic input during waking may be correlated with hyperactivity in mesolimbic DA projections, thus further increasing positive symptomology. Such hyperactivity in mesolimbic DA projections during waking may lead to hypoactivity in mesocortical DA projections to the prefrontal cortex which would further exacerbate negative symptomology and cognitive impairment.

Concluding comments

Ironically, bipolar 'disorder' could actually be an attempt to restore order to schizophrenic disorder. As discussed earlier, there is evidence that schizophrenia is a dynamic condition characterized by interaction effects between modulatory systems. It is, therefore, possible that this inherent dynamism could give rise to an autopoietic response. Such a reaction could be expressed as surges of either aminergic hyperactivity precipitating mania in the waking state or cholinergic hyperactivity producing depression in the waking state or both, resulting in rapid cycling bipolar disorder.

If this hypothesis is correct the most optimistic scenario is that an autopoietic reaction would start early and be successful. If so, only mild depression and/or hypomania may resolve, at least temporarily, a relatively mild case of 'schizophrenia'. There is evidence that bipolar patients in a neutral or hypomanic phrase exhibit increased IQ [74] and enhanced creativity [75]. If the mixed state is more severe then more dramatic manic and depressive reactions may result. In this case the autopoietic response to schizophrenia would take a clearly recognizable form – giving rise to the observation that classic bipolar disorder is diagnostically uncontroversial [7]. Although such a classic response may produce periods of relative normality, the schizophrenic mixed state may return. Thus confirming the observation from clinical practice referred to above, where it was noted that there was sometimes a temporal progression from classic bipolar disorder to schizophrenia but the reverse was rare [13].

Due to the inherent difficulties in imaging and documenting *dynamic* changes in neuromodulatory regulation, there are still profound problems for inductive evidence on the complex dynamics of neuromodulatory systems [31,34]. However, developments in positron emission tomography and single-photon emission computed tomography should render such assessments more productive in the future [34].

Moreover, the phenomenology of schizophrenia has been relatively neglected in psychiatric research [73,76,77]. A comprehensive programme of work that builds on the subjective experience of schizophrenia and bipolar disorder is called for. For example, it was close observation of patients and a careful elucidation of their subjective experience that demonstrated selective attention defects in both schizophrenia and mania, indicating that there are common cognitive deficits in both conditions [7]. More work of this kind has the potential to make a significant contribution to the evidence base on the relationship between the major psychoses.

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