Is Active Psychosis Neurotoxic?

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Positive symptoms of psychosis disrupt mentation. Do they also engineer brain cell death and deterioration? This hypothesis is currently popular as an explanation of the duration of untreated psychosis effect in early schizophrenia. The clinical and neurobiological evidence for its validity is visited and found wanting. Synaptic plasticity, not neurotoxicity, appears to be the mediating process.

Key words: deterioration/duration of untreated psychosis (DUP)/neurodegeneration/synaptic connectivity and plasticity

Introduction

According to Kraepelin,[1] the deterioration process in schizophrenia has always been the cardinal feature of the disorder, the dementia (deterioration) of the praecox era (adolescence). At the turn of the 20th century, all dementing clinical processes, such as Alzheimer disease or syphilis, were accompanied by postmortem evidence of neuronal death. Dementia praecox, therefore, was assumed to be no different, although it took nearly a century of technologic advance to demonstrate brain changes discernable enough to declare with confidence that schizophrenia was a brain disorder.[2,3]

With the recent focus on early detection in schizophrenia and the duration of untreated psychosis (DUP), the original Kraepelinian link between organic brain damage and clinical deterioration arises again. This time, however, the direction of causality is reversed, with the clinical state of psychosis causing neuronal pathology. How has this reversal come about and what is the validity of the hypothesis that active psychosis is neurotoxic? In order to answer or at least to expand on these questions requires exploration of what we know about schizophrenia deterioration both clinically and neuroanatomically, about how the neurotoxic hypothesis came to be, about what we might expect to see clinically and neuropathologically if the untreated clinical state is neurotoxic, and about what we actually see.

Schizophrenic Deterioration: Clinical Manifestations

Schizophrenic deterioration, though a cardinal feature of the disorder, is nevertheless hard to characterize. Unlike other disorders considered to be "neurodegenerative," it starts at the beginning of adulthood, not at the end, and gross memory capacity is generally maintained. In addition to positive symptoms (hallucinations, delusions, and thought disorder), Kraepelin described deterioration as "weak mindedness," a motley and nonspecific mix of "driveling dullness, mannerisms, indifference, lack of volition, poor judgment, diminished work capacity, and overall lack of emotional activity."[4] If consistency exists, it is in the notion of absence, best captured today by the deficit syndrome's primary negative symptoms[5] and by dysregulated behavior that is both overly perseverative and overly random and unpredictable.[6]

Manfred Bleuler[7] endorsed Kraepelin's deteriorated clinical state but emphasized that, at least by his reckoning at mid century, it constituted only about 10% of cases. This suggested that the course and outcome of schizophrenia was no longer uniformly deteriorated as observed by Kraepelin but was decidedly more heterogeneous between individuals. He also noted that within individuals the level of outcome reached was steady over time and relatively impervious to change. He stated, eg, that contemporary treatments had neither succeeded in reducing the ratio of severely deteriorated cases beyond 10% nor increased the number of cases that were "permanently cured."

A review of long-term follow-up studies of schizophrenia from the mid to later 20th century[8] endorsed Bleuler's notion that different levels of symptomatic and functional outcome are reached that are stable and disabled relative to baseline. This suggests that the course of schizophrenia has 2 phases, a time-limited active phase of deterioration and a chronic plateau phase with a resultant level of deterioration that remains stable for years. The neurobiological processes responsible for this deterioration are currently speculative and include theories of developmentally determined changes in synaptic connectivity gone awry[9] in addition to theories of neurodegeneratively driven brain damage.[10]

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Clinical natural history suggests that this "window of deterioration" is developmentally linked (adolescence) and time limited. It begins around the first psychotic episode and usually in the late prodromal phase.[11] The follow-up study review[8] estimated that this phase could last 5–10 years postonset. A review of a chronic schizophrenic sample with abundant retrospective data about the development of illness from the first break forward suggests that deterioration is most apparent in the first 3 years of active illness.[12] Presumably, the functional plateau that ensues is correlated with a cessation of the developmentally linked brain changes as well.

More data would be welcome about the nature, timing, and phenomenology of this window of deterioration. Furthermore, recent work suggests that different domains of psychopathology have different windows. Mason et al,[13] eg, noted that deterioration in social functioning is limited to the first year after onset. Neurocognitive functioning, in contrast, apparently deteriorates in the late premorbid and prodromal periods but not after onset.[14–16]

Schizophrenia Deterioration: Neuroanatomical Manifestations

The clinical manifestations of schizophrenia rest on more than a century of observations. In contrast, the neuroanatomical manifestations of the disorder derive from data spanning less than a generation. The data that have been produced support a picture of reduced synaptic connectivity between brain neurons rather than a reduction in the number of neurons. Postmortem histopathologic investigations found reduced spine densities and smaller dendritic arbors on the pyramidal cells of the cortex in schizophrenia.[17–20] The most replicated postmortem finding has been increased neuronal density in the cortex resulting from reduced neuropil without neuronal loss.[2,3,21–24]

These postmortem findings for schizophrenia appear milder than the findings for classically neurodegenerative disorders such as Alzheimer's, with its neuronal cell loss and reactive gliosis. Given the severity that schizophrenic clinical deterioration can reach, the telltale signs of outright neurodegeneration were assumed to exist and were sought for time and again, but to no avail, leading experts in the field to conclude that postmortem neuropathology of schizophrenia yields no specific cell phenotype, no gliosis, and little to no cell loss.[25,26]

The Neurotoxicity Hypothesis: Origins

The origins of the hypothesis that untreated psychosis is neurotoxic probably begin with Wyatt's now classical article on neuroleptics and the natural course of schizophrenia.[27] He reviewed virtually every treatment study of schizophrenic patients in the transition periods before, during, and after the introduction of antipsychotic medications. Most of the studies conducted (and reviewed) compared different cohorts of patients (pre- and postneuroleptic), not single cohorts randomized to drug vs no drug. Many studies also collected longitudinal data sufficient to characterize and compare the long-term courses of these samples. The data collectively documented a robustly positive effect of antipsychotic treatment not only for short-term symptom remission but also for longer term outcome. From these data, Wyatt postulated that antipsychotics both treated active psychotic symptoms and prevented deterioration. On the basis of this article, the term "untreated psychosis" came to mean untreated with antipsychotics, and on the basis of this article the neurotoxicity hypothesis was born: "While psychosis is undoubtedly demoralizing and stigmatizing, it may also be biologically toxic."[27]

The notion that psychosis untreated by antipsychotics might be toxic was bolstered by longitudinal studies of first-episode schizophrenic samples. Loebel et al[28] documented that longer periods of psychosis untreated by antipsychotics correlated significantly with poorer outcome. Lieberman[29,30] noted in the same sample that the number of relapses into active psychosis postonset was associated with greater treatment resistance, eg, longer time to remission and attenuated clinical response, with each subsequent treatment. The data appeared to support a negative dose effect of active psychosis on long-term course, ie, that active (positive symptom) psychosis was toxic to brain. These articles, plus the work from the first-episode Early Psychosis Prevention and Intervention Center program in Melbourne,[31] soon made the DUP a focus of intense investigation.

The hypothesis that psychotic symptoms, particularly positive symptoms, can cause deterioration in schizophrenia is reasonable but must be based on more than a correlation. For example, testing this causal hypothesis requires disproving the alternate hypothesis that a person who is genetically and neurobiologically vulnerable to a more severe form of schizophrenia develops the overt disorder in ways that lead to later identification and treatment.[32] However, testing this alternate hypothesis that prognosis, ie, vulnerability to psychosis severity, determines DUP rather than vice versa is methodologically challenging. It requires the prospective prediction of schizophrenia caseness and of DUP by measures of premorbid prognosis in nonsymptomatic samples. In essence, it requires the long-term follow along of a very large prospective birth cohort sample. It is clear why an effort of such daunting proportions has never been conducted in contrast to replicating the DUP-outcome correlation which requires at the least measuring only 2 variables, DUP and some index of outcome, which can be done in one interview. Such methodological ease has given rise to a tidal wave of "DUP studies," most of which replicate the positive correlation between

longer DUP and poorer outcome. These replications do not extend knowledge, but their sheer number add weight to the assumption that a causal relationship has been proven and that it is in the direction of longer untreated psychosis causing poorer outcome.

Neurotoxic Untreated Psychosis: Nonvalidated Corollary Predictions

What might we expect to see vis-a-vis the course of schizophrenia if active psychosis were indeed neurotoxic? First, the DUP effect would not reach an asymptote at longer DUPs, ie, it would not plateau. This is not observed. In fact, the differences in outcome between a long DUP and a DUP twice as long are minimal, suggesting that if active symptoms are toxic they are more so early on in the disorder, and this difference needs to be accounted for. Second, if active psychosis were neurotoxic, deterioration would not start before the advent of positive psychotic symptoms, and we know this is not the case with at least one domain of brain functioning, ie, neurocognitive capacity, which deteriorates before onset.[14,15] Third, if active psychosis were neurotoxic, we would also expect that the relapse-dose effect described by Lieberman[29,30] would continue beyond the window of functional deterioration. In fact, if untreated psychosis were neurotoxic, we would not expect to see a plateauing of deterioration at all. Instead, each new relapse into active psychosis would leave the brain with less neuronal reserve, and functional deficits would accrue in direct proportion to the "dose" of positive symptoms, ie, their longevity and intensity. Yet we know that this plateau in functional capacity is ubiquitous to schizophrenia and that once the plateau is reached the relapse-dose effect attenuates. Clinicians of chronic schizophrenic patients, eg, know that time to remission following relapse varies little within the same patient.[33] From the clinical course perspective alone, then, we can say that active psychosis is not neurotoxic because schizophrenic deterioration does not go "all the way" like other neurodegenerative disorders such as Alzheimer disease or Huntington chorea. Once the plateau is reached, the positive symptoms of schizophrenia neither become more and more severe nor become harder to treat after each relapse.

What might we expect to see neuropathologically if untreated psychosis were neurotoxic? Like other neurodegenerative disorders, we would expect to see evidence of neuronal death in the form of fewer cortical neurons and/or gliosis as a reaction to neuronal death. Even if certain forms of apoptosis do not generate a glial reaction,[34] the neuronal count would still be lower. The postmortem brains of schizophrenic patients, as noted above, show neither gliosis nor loss of neuronal cell numbers.[25,35] Neuropathology, like longitudinal course, does not support the hypothesis that untreated psychosis is neurotoxic.

Alternate Hypothesis to Neurotoxicity: Psychosis as Reduced Connectivity

The synaptic plasticity hypothesis surmises that the neuropathology of schizophrenia centers around significantly reduced neuropil, ie, the synaptic syncytium between neurons.[36] It has been shown that schizophrenia symptom formation (eg, hallucinations) can be simulated in computer models by reducing the connections within a putative neuronal network.[37] In this model of schizophrenia as a disorder of reduced synaptic connectivity,[9] the theory assumes that reduced connectivity precedes symptom formation and is generative of characteristic symptoms.

The question raised here is whether symptom formation, once extant, can change levels of connectivity among neurons via negative and positive information feedback loops. For example, could chronic and intense preoccupation with positive symptoms, eg, a delusional schema, decrease the use of other brain circuits leading to content-driven alterations in connectivity, ie, disuse atrophy in some circuits and overuse hypertrophy in other circuits, resulting either in a net loss of connections and a system blighted with negative symptoms or in a maldistribution of connections and a system with less cognitive capacity, reserve, and flexibility?

In such a system, any treatment (including antipsychotics) that reduces psychotic symptoms might also release the brain from its aberrant, symptom generating, wiring, and reengage the patient in a cognitive dialogue with the real world as opposed to a world of psychotic creations. Reunion with reality reestablishes a richer fabric of complimentary neuronal connectivity. It may be in this way that Wyatt's[27] notion of drugs changing the natural history of schizophrenia has merit, insofar as drugs reconnect the patient quickly with the real world and prevent the backward loss of connections between patient and the daily challenge of adapting to reality. Time and degree of immersion in a mental state of psychosis is the culprit here, leading to atrophy of worldly-wise judgment and skills and to atrophy of the synaptic connections underpinning these skills. The culprit is not the psychotic state killing neuronal cells (unless suicide intervenes). Antipsychotic medication works, in contrast, by reengaging the patient in the world on a more complex level with greater investment and cathexis, not by being "neuroprotective." The process mediating these changes, both destructive and ameliorative, is the process of learning, ie, changing synaptic plasticity,[38] not changing neuronal number.

Conclusion

Acutely active psychosis is a dangerous mental state, if not a medical emergency, because of its aberrant experiences, loss of insight, and distortions of judgment. It

requires immediate treatment, including antipsychotic medication, to reduce the danger of such distortions to life and social network. The threat of chronically active psychosis is time rather than mortality and stigma, time immersed in the negative symptoms or cognitive distortions of disorder. If prolonged, it may well create deficits that add to severity beyond the level ultimately determined by the original brain pathophysiology. Whether these further deficits result from brain-damaging neurotoxicity or from attenuated synaptic plasticity secondary to withdrawal from daily commerce is the question posed here. The evidence thus far appears to point to the latter explanation and to endorsing treatment strategies that try first to minimize psychotic distortions with asylum and medication and then to maximize reengagement with reality via outreach strategies and medications that together preserve salience and promote real world investment.

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