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Part I

Introduction

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Introduction: is psychosis a neurobiological syndrome?

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Psychosis is a state in which the individual experiences a severe disconnection from reality. The most common symptoms associated with psychotic disorders are delusions and hallucinations. Delusions are false beliefs about experiences, oneself, or the environment that cannot be altered in the face of contradictory evidence. An example would be delusions of persecution in which the individual believes that others are tormenting, ridiculing, or intending to harm him or her. Hallucinations involve false perceptions in any sensory modality without insight into their pathological nature. The most common hallucination is auditory, which is generally experienced as "hearing voices." Other symptoms associated with psychotic disorders include negative symptoms such as restricted emotional expression (flat affect), sparse language output (alogia), poor initiation and persistence of goal-directed behaviors (avolition), disorganized thoughts, speech, or behaviors, or a severe decrease in reactivity to one's surroundings (catatonia) (American Psychiatric Association, 2000).

Psychosis has many etiologies. The Diagnostic and Statistical Manual-IV Text Revision (DSM-IV TR) (American Psychiatric Association, 2000) distinguishes between primary psychotic disorders and those due to other etiologies. Primary psychotic disorders include schizophrenia, delusional disorders, schizoaffective disorder, schizophreniform disorder, and brief psychotic disorder. By contrast, psychosis can be due to a general medical condition such as Dementia of the Alzheimer's Type (DAT) or traumatic brain injury (TBI), a psychoactive substance such as amphetamines or cannabis, or secondary to a mood disorder such as major depression. The following are brief descriptions of the DSM-IV TR diagnostic criteria for each disorder:

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Diagnostic criteria for schizophrenia

A. Two or more of the following symptoms are present: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, and (5) negative symptoms.
B. Dysfunction in social, academic, or occupational achievement.
C. Continuous signs of the illness persist for at least six months.
D. Exclusion of schizoaffective or mood disorder as an etiology.
E. Exclusion of substance use or a general medical condition as an etiology.
F. If a premorbid pervasive developmental disorder exists, hallucinations and delusions are present for at least a month to warrant and additional diagnosis of schizophrenia.

Diagnostic criteria for psychotic disorder due to a general medical condition

A. Prominent hallucinations or delusions are present.
B. There is evidence that the psychotic symptoms are a direct consequence of a general medical condition.
C. Psychotic symptoms are not better accounted for by another mental disorder.
D. Psychotic symptoms do not occur exclusively during the course of a delirium.

Diagnostic criteria for substance-induced psychotic disorder

A. Prominent hallucinations or delusions are present.
B. There is evidence that the psychotic symptoms develop within a month of substance intoxication or withdrawal, or the substance is etiologically related to the psychosis.
C. Psychotic symptoms are not better accounted for by another mental disorder.
D. Psychotic symptoms do not occur exclusively during the course of a delirium.

There exists a curious dichotomy in DSM-IV TR criteria between the primary psychotic disorders and Psychotic Disorders Due to a General Medical Condition (PDDGMC) and Substance-Induced Psychotic Disorders (SIPD). In both PDDGMC and SIPD, diagnosis is based on the presence of psychotic symptoms (criterion A) within the context of either a medical condition or substance use (criterion B), while ruling out schizophrenia or delirium as the

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cause of the psychosis (criteria C and D). Thus in these two diagnostic categories, the etiology of psychotic symptoms is "known," while other mental disorders must be ruled out as the cause. By contrast, for primary psychotic disorders, diagnosis is based upon the presence of psychotic symptoms (criteria A and F), the severity and duration of illness (criteria B and C), and ruling out other etiologies (criteria D and E). Thus unlike PDDGMC or SIPD in which the clinician must establish an etiology to make a diagnosis, for the primary psychotic disorders, the etiological concern of the clinician is to rule out other etiologies as causative. If this can be accomplished, then it is assumed that psychosis is due to schizophrenia.

The DSM-IV TR nomenclature for psychosis illustrates a major criticism of the classification scheme in general. Unlike general medical disease models, psychiatric diagnoses are often based upon symptom clusters rather than tied to etiology (Pichot, 1994). Indeed, on a practical level, the symptom-based nosology of the DSM-IV TR frequently results in diagnostic dilemmas for clinicians as the presentation of primary and other psychotic disorders are often very similar. For example, the modal patient with psychosis due to cocaine or methamphetamine use, seizure disorder, or TBI generally resembles a patient with schizophrenia, paranoid type (Fujii & Ahmed, 2002a; Post & Kopanda, 1976; Sachdev, 1998; Sato, Numachi & Hamamura, 1992). In addition, studies have found that there is no symptom specific to schizophrenia. Even the once hypothesized schizophrenic marker, Schneiderian First Rank Signs (Schneider, 1959), can be found in bipolar disorder and psychotic disorders of other etiologies (Gonzalez-Pinto *et al.*, 2003; Marneros, 1988; Sato *et al.*, 1992).

The following hypothetical case illustrates how similar presentations and different criteria (etiology versus severity/duration of symptoms) can cause problems with differential diagnoses. Let's say Fred, a 25-year-old male without a previous history of psychosis, comes to the ER for paranoid delusions and auditory hallucinations. He has used methamphetamine daily over a five-year period and is currently intoxicated with methamphetamine. In this case, his diagnosis would most likely be methamphetamine-induced psychosis as the onset of psychosis can clearly be tied to his drug use. By contrast, let's say that Fred continues to experience paranoid delusions six months after abstinence. According to the methamphetamine literature, it is not uncommon for long-term users to remain symptomatic six months after discontinuing their use (Sato *et al.*, 1992). However, according to DSM-IV TR differential diagnosis recommendations, in this case schizophrenia would have to be considered as the diagnosis due to duration of illness, even if there is no family history of schizophrenia and there is a known potential etiology.

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Conversely, let's say that Fred's cousin has been diagnosed with schizophrenia. Fred's family predisposition may suggest that he suffers from a primary psychotic disorder. On the other hand, studies have reported that a family history of schizophrenia is a risk factor for substance-induced psychosis such as hallucinogens and cannabis (Tsuang, Simpson, & Kronfold, 1982). Given the fact that monozygotic twins have only a 50% concordance rate for schizophrenia (Gottesman, 1991), environmental events such as the use of methamphetamine may be required to trigger schizophrenia in a genetically vulnerable individual. Thus, in this case, is methamphetamine an environmental factor that triggers the onset of schizophrenia or is it the etiology of the psychosis? How can you rule out which etiology is causative? To further cloud matters, what if Fred were 45 years old instead of 25? Would this affect which etiology is more salient? What if Fred sustained a previous head injury with a seven-day loss of consciousness three months prior to the onset of his delusions and hallucinations? Would the head injury be the etiology of psychosis, the trigger of a schizophrenia episode, a coincidental occurrence, or perhaps a contributing factor to a psychosis? What if he didn't lose consciousness? In such a case, it would be extremely difficult to rule out schizophrenia, TBI, or methamphetamine as being the primary etiology of the psychosis, rule outs being an essential criterion for each DSM-IV TR category of psychotic disorder.

Unfortunately, these issues are not uncommon as about 50% of people who are diagnosed with schizophrenia also have a substance abuse problem (Regier *et al.*, 1990), whereas up to 40% have sustained head injuries (for a review see Fujii, 2005). In such cases, studies have shown that patients who meet criteria for GMC and SIPD are often diagnosed with schizophrenia (Fujii & Ahmed, 2002a; Shaner *et al.*, 1998).

Again going back to the DSM-IV TR, diagnostic issues arise because the presentation of schizophrenia is not unique, as no symptom is pathognomonic of the illness. Similarly there is not a definitive biological marker to designate the presence of schizophrenia. Instead, diagnosis is primarily based upon the presence and severity of psychotic symptoms in which no other etiology can be identified. Furthermore, although researchers agree that genetic factors are more important than environmental factors in the transmission of schizophrenia, more than 60% of people with schizophrenia have no family history (Gottesman, 1991). A diagnosis of schizophrenia essentially does not tell us anything about the etiology of the psychosis. Indeed, many speculate that schizophrenia is a heterogeneous illness with more than one etiology (Schroder *et al.*, 1995; Seaton, Goldstein, & Allen, 2001).

Due to the inherent problems in DSM-IV TR nomenclature for psychotic disorders, we offer a different conceptual approach. We argue that the separate

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categories (primary and other) of psychotic disorders may be a distinction without a difference, as many GMC and SIPD appear to affect the same neurochemical systems and have similar neuropathology to schizophrenia (Fujii & Ahmed, 2004). Schizophrenia has consistently been associated with abnormalities in mesial temporal, frontal areas, and frontal-temporal connectivity (McCarley *et al.*, 1999; Berman & Meyer-Lindenberg, 2004), as well as the dopaminergic system projecting from the ventral tegmental area to the striatum (for a review see Thompson, Pogue-Geile, & Grace, 2005). Among the most common medical etiologies associated with secondary psychosis include disorders affecting temporal structures such as DAT, TBI, and temporal lobe epilepsy (Wragg & Jeste, 1989; Sachdev, 1998; Fujii & Ahmed, 2002a). Similarly, substances that directly affect the transmission of dopamine such as cocaine, methamphetamine, and anti-Parkinsonian medications have been found to induce psychoses in users (Cummings, 1991; Post and Kopanda, 1976; Sato *et al.*, 1992). Furthermore, in many GMC and SIPD a family history of schizophrenia is a risk factor (Sachdev, Smith, & Cathcart 2001; Tsuang *et al.*, 1982).

With other neurological syndromes, lesions to specific areas of the brain are associated with concomitant behavioral, emotional, and cognitive sequelae regardless of etiology (Mesulam, 2000). For example, subcortical lesions generally present with cognitive slowing, deficits in attention and concentration, executive functioning, visuospatial skills, and memory, with more problems in retrieval versus memory encoding and storage problems. There is an absence of aphasia, apraxia, and agnosia, and apathy, depression, or personality changes (Lezak, Howieson, & Loring, 2005). Severity of injury is also important for presentation and may be more important than actual etiology in determining presentation. This principle was demonstrated in a study comparing the effects of anoxia versus TBI that found cognition is more closely associated with severity of injury than with etiology (Hopkins, Tate, & Bigler, 2005). In addition, there is emerging evidence indicating that neuropathology resulting in associated sequelae occur in other "psychiatric" disorders such as depression. For example, Hickie *et al.* (2005) reported that reduced hippocampal volumes in depression are associated with deficits in visual and verbal memory. Given that schizophrenia is a brain disease, why shouldn't the same principles apply to psychosis?

We propose an alternate conceptualization of psychosis. We argue that psychosis is a neurobiological syndrome similar to aphasia and apraxia. Affected structures include frontal systems that would include the frontal-striatal-thalamic-cerebellar axis as well as the frontal-striatal-hippocampal axis, and the dopaminergic projections to these areas. Altering this circuit to a significant degree by any

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means including drugs, disease, trauma, or normal developmental brain changes can result in psychotic symptoms. Our conceptual framework for developing a psychotic disorder is as follows (Fujii & Ahmed, 2002b):

1. Psychosis is associated with abnormal functioning of frontal systems, temporal lobes, and the dopaminergic projections to these areas.
2. All individuals are at risk for developing a psychosis. Contributing factors include:
   a. genetic predisposition.
   b. environmental factors.
      i. damage sustained through trauma, disease, substance abuse.
      ii. effects of experience on neuronal structures and neurochemical release.
   c. neuronal and biochemical changes during normal human development.
3. Psychosis will develop when a threshold of damage or changes to frontal systems, temporal structures, and dopaminergic projections is attained.

In this framework, anyone would be vulnerable to developing a psychosis once a threshold of damage or changes to the affected structures is reached. For example, if there is a strong genetic predisposition, the onset of psychosis may be inevitable after neuronal pruning during adolescence/early adulthood, or may be expedited with onset in adolescence by an early mild head injury or marijuana abuse. Conversely, for a person with no genetic vulnerability, psychosis may occur in middle age only after multiple head injuries and long-term methamphetamine dependence, or in late life after the onset of DAT. In both cases, life experiences that increase stress or stress response that would in turn increase the amount of dopamine in the brain would also contribute to the initial onset of psychosis or exacerbation of illness.

This framework is consistent with the diathesis–stress model of schizophrenia which hypothesizes that the disorder results from an interaction between a biological predisposition and an environmental trigger (Zubin & Spring, 1977). Our model, however, differs in several key aspects: (1) it applies a similar conceptualization to psychotic disorders in general, (2) it specifies and expands potential environmental factors beyond the pre- and perinatal periods, and (3) it also incorporates the effects of normal life-cycle neurological changes in conceptualization beyond young adulthood.

Our model is also consistent with newer models of vulnerability for schizophrenia focusing on endophenotypes. For example, Weiser, van Os, & Davidson (2005) argues that impaired cognition is present in both patients with schizophrenia and their first degree relatives more frequently than in the normal population. These broad vulnerabilities, or endophenotypes, are believed to be genetically transmitted. In our conceptual framework,

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we argue that vulnerabilities such as impaired cognition can also result from environmental factors. For a more in-depth discussion of the model see Fujii & Ahmed (2002b).

Examining the hypothesis

One purpose of the book is to examine the Fujii & Ahmed (2004) hypothesis that psychosis is a neurobiological syndrome. A neurobiological syndrome exists if the following criteria are met:

1. A constellation of symptoms is reliably associated with neuropathology in a circumscribed structural location or neural circuit.
2. Similar neurobiological disturbances (location or neural circuit) secondary to different etiologies would result in similar cognitive or behavioral symptoms.
3. Smaller amounts of similar neurobiologic disturbances are associated with milder symptoms.
4. Additional symptoms such as cognitive, mood, psychiatric, or other associated neurological symptoms are related to other networks simultaneously being affected by underlying neurochemical or neuropathologic processes.
5. Aside from treating the underlying disease process, treatment for the associated symptoms of a neurobiological disorder of different etiologies is similar.

This hypothesis will be examined by comparing and contrasting the characteristics of psychotic disorders of different etiologies. If psychosis is a neurobiological syndrome, then psychotic disorders of different etiologies should affect common brain structures and neurochemical systems, and should also overlap in symptoms and presentation. Each chapter will review the literature on a psychotic disorder of a specific etiology. Data in the following areas will be reviewed: (1) epidemiology, (2) age of onset, (3) presentation (positive and negative symptoms, neuropsychological deficits, emotional disorders), (4) course and progression including latency from initial insult to presentation of psychotic symptoms and prodrome, (5) suspected neuropathology, (6) suspected neurochemical pathology, (7) genetic factors, (8) other risk factors, and (9) treatment. In addition, the data for each area will be rated on the quality of evidence according to the Centre for Evidence-Based Medicine Levels of Evidence Grades of Recommendation System criteria (see Appendix at the end of chapter for criteria). This rating is included to inform the reader of the current status of evidence for a specific etiology of psychosis.

The data will be evaluated qualitatively for similarities and differences of the aforementioned nine areas between the different etiologies of psychosis. By comparing this information we hope to gain insight into which brain areas are associated with psychosis and patterns in development, presentation,

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and treatment. These qualitative impressions will be described section by section in the concluding chapter.

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