

CHAPTER 1

Psychosis and Schizophrenia

- Symptom dimensions in schizophrenia
 - Clinical description of psychosis
 - Schizophrenia is more than a psychosis
 - Beyond positive and negative symptoms of schizophrenia
 - Symptoms of schizophrenia are not necessarily unique to schizophrenia
 - Brain circuits and symptom dimensions in schizophrenia
- Neurotransmitters and circuits in schizophrenia
 - Dopamine
 - Dopaminergic neurons
 - Key dopamine pathways in the brain
 - The integrated dopamine hypothesis of schizophrenia
 - Glutamate
 - Glutamate synthesis
 - Synthesis of glutamate cotransmitters glycine and d-serine
 - Glutamate receptors
 - Key glutamate pathways in the brain and the NMDA receptor hypofunction hypothesis of schizophrenia
- Neurodegenerative hypothesis of schizophrenia
 - Excitotoxicity and the glutamate system in neurodegenerative disorders such as schizophrenia
- Neurodevelopmental hypothesis and genetics of schizophrenia
 - Is schizophrenia acquired or inherited?
 - Genes that affect connectivity, synaptogenesis and NMDA receptors
 - Dysconnectivity
 - Abnormal synaptogenesis
 - NMDA receptors, AMPA receptors, and synaptogenesis
 - Convergence of susceptibility genes for schizophrenia upon glutamate synapses
 - The bottom line
- Neuroimaging circuits in schizophrenia
- Summary

Psychosis is a difficult term to define and is frequently misused, not only in the newspapers, in movies, and on television but unfortunately among mental health professionals as well. Stigma and fear surround the concept of psychosis, and the average citizen worries about long-standing myths of “mental illness,” including “psychotic killers,” “psychotic rage,” and the equivalence of “psychosis” with the pejorative term “crazy.”

There is perhaps no area of psychiatry where misconceptions are greater than in that of psychotic illnesses. The reader is well served to develop an expertise on the facts about

the diagnosis and treatment of psychotic illnesses in order to dispel unwarranted beliefs and to help destigmatize this devastating group of illnesses. This chapter is not intended to list the diagnostic criteria for all the different mental disorders of which psychosis is either a defining or associated feature. The reader is referred to standard reference sources (DSM-IV and ICD-10) for that information. Although schizophrenia is emphasized here, we will approach psychosis as a syndrome associated with a variety of illnesses that are all targets for antipsychotic drug treatment.

Symptom dimensions in schizophrenia

Clinical description of psychosis

Psychosis is a syndrome – a mixture of symptoms – that can be associated with many different psychiatric disorders, but it is not a specific disorder itself in diagnostic schemes such as DSM-IV or ICD-10. At a minimum, psychosis means delusions and hallucinations. It generally also includes symptoms such as disorganized speech, disorganized behavior, and gross distortions of reality testing.

Therefore psychosis can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others is impaired. Psychotic disorders have psychotic symptoms as their defining features; there are, however, other disorders in which psychotic symptoms may be present but are not necessary for the diagnosis.

Those **disorders that require the presence of psychosis** as a *defining* feature of the diagnosis include schizophrenia, substance-induced (i.e., drug-induced) psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, and psychotic disorder due to a general medical condition (Table 1-1). **Disorders that may or may not have psychotic symptoms** as an *associated* feature include mania and depression as well as several cognitive disorders such as Alzheimer's dementia (Table 1-2).

Psychosis itself can be paranoid, disorganized/excited, or depressive. Perceptual distortions and motor disturbances can be associated with any type of psychosis. **Perceptual distortions** include being distressed by hallucinatory voices; hearing voices that accuse, blame, or threaten punishment; seeing visions; reporting hallucinations of touch, taste, or odor; or reporting that familiar things and people seem changed. **Motor disturbances** are peculiar, rigid postures; overt signs of tension; inappropriate grins or giggles; peculiar

TABLE 1-1 Disorders in which psychosis is a defining feature

Schizophrenia
Substance-induced (i.e., drug-induced) psychotic disorders
Schizophreniform disorder
Schizoaffective disorder
Delusional disorder
Brief psychotic disorder
Shared psychotic disorder
Psychotic disorder due to a general medical condition

TABLE 1-2 Disorders in which psychosis is an associated feature

Mania
Depression
Cognitive disorders
Alzheimer's dementia

repetitive gestures; talking, muttering, or mumbling to oneself; or glancing around as if hearing voices.

In **paranoid psychosis**, the patient has paranoid projections, hostile belligerence, and grandiose expansiveness. **Paranoid projection** includes preoccupation with delusional beliefs; believing that people are talking about oneself; believing one is being persecuted or being conspired against; and believing that people or external forces control one's actions. **Hostile belligerence** is a verbal expression of feelings of hostility; expressing an attitude of disdain; manifesting a hostile, sullen attitude; manifesting irritability and grouchiness; tending to blame others for problems; expressing feelings of resentment; complaining and finding fault; as well as expressing suspicion of people. **Grandiose expansiveness** is exhibiting an attitude of superiority; hearing voices that praise and extol; and believing one has unusual powers, is a well known personality, or has a divine mission.

In a **disorganized/excited psychosis**, there is conceptual disorganization, disorientation, and excitement. **Conceptual disorganization** can be characterized by giving answers that are irrelevant or incoherent, drifting off the subject, using neologisms, or repeating certain words or phrases. **Disorientation** is not knowing where one is, the season of the year, the calendar year, or one's own age. **Excitement** is expressing feelings without restraint, manifesting speech that is hurried, exhibiting an elevated mood, showing an attitude of superiority, dramatizing oneself or one's symptoms, manifesting loud and boisterous speech, exhibiting overactivity or restlessness, and exhibiting excess of speech.

Depressive psychosis is characterized by retardation, apathy, and anxious self-punishment and blame. **Retardation and apathy** are manifesting slowed speech, indifference to one's future, fixed facial expression, slowed movements, deficiencies in recent memory, blocking in speech, apathy toward oneself or one's problems, slovenly appearance, low or whispered speech, and failure to answer questions. **Anxious self-punishment and blame** is the tendency to blame or condemn oneself; anxiety about specific matters; apprehensiveness regarding vague future events; an attitude of self-deprecation; manifesting a depressed mood; expressing feelings of guilt and remorse; preoccupation with suicidal thoughts, unwanted ideas, and specific fears; and feeling unworthy or sinful.

This discussion of clusters of psychotic symptoms does not constitute diagnostic criteria for any psychotic disorder. It is given merely as a description of several types of symptoms in psychosis to give the reader an overview of the nature of behavioral disturbances associated with the various psychotic illnesses.

Schizophrenia is more than a psychosis

Although schizophrenia is the commonest and best known psychotic illness, it is not synonymous with psychosis but is just one of many causes of psychosis. Schizophrenia affects 1 percent of the population, and in the United States there are over 300,000 acute schizophrenic episodes annually. Between 25 and 50 percent of schizophrenia patients

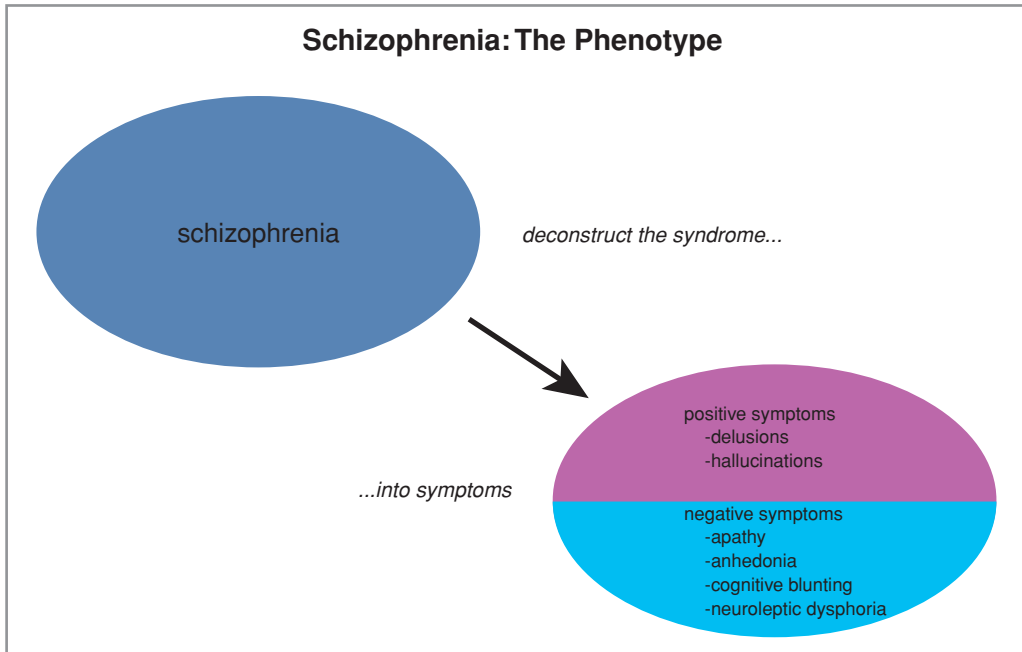


FIGURE 1-1 Positive and negative symptoms. The syndrome of schizophrenia consists of a mixture of symptoms that are commonly divided into two major categories, positive and negative. Positive symptoms, such as delusions and hallucinations, reflect the development of the symptoms of psychosis; they can be dramatic and may reflect loss of touch with reality. Negative symptoms reflect the loss of normal functions and feelings, such as losing interest in things and not being able to experience pleasure.

attempt suicide, and 10 percent eventually succeed, contributing to a mortality rate eight times greater than that of the general population. The life expectancy of a schizophrenic patient may be 20 to 30 years shorter than that of the general population, not only due to suicide but in particular due to premature cardiovascular disease. Accelerated mortality from premature cardiovascular disease in schizophrenic patients is caused not only by genetic factors and lifestyle choices – such as smoking, unhealthy diet, and lack of exercise leading to obesity and diabetes – but also, unfortunately, by treatment with some antipsychotic drugs, which themselves cause an increased incidence of obesity and diabetes and thus increased cardiac risk. In the United States, over 20 percent of all social security benefit days are used for the care of schizophrenic patients. The direct and indirect costs of schizophrenia in the United States alone are estimated to be in the tens of billions of dollars every year.

Schizophrenia by definition is a disturbance that must last for 6 months or longer, including at least 1 month of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. Thus, symptoms of schizophrenia are often divided into positive and negative symptoms (Figure 1-1).

Positive symptoms are listed in Table 1-3. These symptoms of schizophrenia are often emphasized, since they can be dramatic, can erupt suddenly when a patient decompensates into a psychotic episode (often called a psychotic “break,” as in break from reality), and are the symptoms most effectively treated by antipsychotic medications. **Delusions** are one type of positive symptom; these usually involve a misinterpretation of perceptions or experiences. The most common content of a delusion in schizophrenia is persecutory, but

TABLE 1-3 Positive symptoms of psychosis and schizophrenia

Delusions
Hallucinations
Distortions or exaggerations in language and communication
Disorganized speech
Disorganized behavior
Catatonic behavior
Agitation

TABLE 1-4 Negative symptoms of schizophrenia

Blunted affect
Emotional withdrawal
Poor rapport
Passivity
Apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity
Stereotyped thinking
Alogia: restrictions in fluency and productivity of thought and speech
Avolition: restrictions in initiation of goal-directed behavior
Anhedonia: lack of pleasure
Attentional impairment

may comprise a variety of other themes including referential (i.e., erroneously thinking that something refers to oneself), somatic, religious, or grandiose. **Hallucinations** are also a type of positive symptom (Table 1-3) and may occur in any sensory modality (e.g., auditory, visual, olfactory, gustatory and tactile), but auditory hallucinations are by far the most common and characteristic hallucinations in schizophrenia. Positive symptoms generally reflect an **excess** of normal functions and, in addition to delusions and hallucinations, may also include distortions or exaggerations in language and communication (disorganized speech) as well as in behavioral monitoring (grossly disorganized or catatonic or agitated behavior).

Negative symptoms are listed in Tables 1-4 and 1-5. Classically, there are at least five types of negative symptoms, all starting with the letter “A” (Table 1-5):

alogia – dysfunction of communication; restrictions in the fluency and productivity of thought and speech

affective blunting or flattening – restrictions in the range and intensity of emotional expression

asociality – reduced social drive and interaction

anhedonia – reduced ability to experience pleasure

avolition – reduced desire, motivation, or persistence; restrictions in the initiation of goal-directed behavior

TABLE 1-5 What are negative symptoms?

Domain	Descriptive Term	Translation
Dysfunction of communication	Alogia	Poverty of speech; e.g., talks little, uses few words
Dysfunction of affect	Blunted affect	Reduced range of emotions (perception, experience and expression); e.g., feels numb or empty inside, recalls few emotional experiences good or bad
Dysfunction of socialization	Asociality	Reduced social drive and interaction; e.g., little sexual interest, few friends, little interest in spending time with (or little time spent with) friends
Dysfunction of capacity for pleasure	Anhedonia	Reduced ability to experience pleasure; e.g., finds previous hobbies or interests unpleasurable
Dysfunction of motivation	Avolition	Reduced desire or motivation persistence; e.g., reduced ability to undertake and complete everyday tasks; may have poor personal hygiene

Negative symptoms in schizophrenia are commonly considered a reduction in normal functions, such as blunted affect, emotional withdrawal, poor rapport, passivity and apathetic social withdrawal, difficulty in abstract thinking, stereotyped thinking and lack of spontaneity. These symptoms are associated with long periods of hospitalization and poor social functioning. Although this reduction in normal functioning may not be as dramatic as positive symptoms, it is interesting to note that negative symptoms of schizophrenia determine whether a patient ultimately functions well or has a poor outcome. Certainly patients will have disruptions in their ability to interact with others when their positive symptoms are out of control, but their degree of negative symptoms will largely determine whether they can live independently, maintain stable social relationships, or reenter the workplace.

Negative symptoms in schizophrenia can be either primary or secondary (Table 1-6). Primary negative symptoms are considered to be those that are core features of the primary deficits of schizophrenia itself. Other deficits of schizophrenia that may manifest themselves as negative symptoms are thought to be secondary to the positive symptoms of psychosis or secondary to EPS (extrapyramidal symptoms) caused by antipsychotic medications. Negative symptoms can also be secondary to depressive symptoms or environmental deprivation. As shown in Table 1-6, there is debate as to whether this distinction of primary from secondary negative symptoms is important.

Since negative symptoms are so important to the outcome of schizophrenia, it is important to measure them in clinical practice (Table 1-7). Although formal rating scales such as those listed in Table 1-8 can be used to measure negative symptoms in research studies, in clinical practice it may be more practical to identify and monitor negative symptoms quickly by observation alone (Figure 1-2) or by some simple questioning (Figure 1-3). A more quantitative assessment for clinical practice can be rapidly made by rating just four items taken from formal rating scales and shown in Table 1-9; namely, reduced range of emotions, reduced interests, reduced social drive, and restricted speech quantity.

Negative symptoms are not just part of the syndrome of schizophrenia – they can also be part of a “prodrome” that begins with subsyndromal symptoms which do not meet the diagnostic criteria of schizophrenia and occur before the onset of the full syndrome (Figure 1-4). Prodromal negative symptoms are important to detect and monitor over time in

TABLE 1-6 Primary and secondary negative symptoms**Primary:** Inherent to the disease process itself**Secondary:** Result from other factors, such as depression, extrapyramidal symptoms (EPS), suspicious withdrawal**Deficit syndrome:** Enduring primary negative symptoms**Is the distinction important?****YES**

Secondary can mimic primary negative symptoms

e.g., unresponsive facial expression:

- Sign of reduced emotional responsiveness and experience, anhedonia?
- Result of EPS?

NO

Negative symptoms, whether primary or secondary, still impair outcomes and should be avoided

TABLE 1-7 Why measure negative symptoms?

1. In clinical trials
 - To measure efficacy of interventions in treating negative symptoms
 - pharmacological interventions
 - psychosocial, cognitive, and behavioral interventions
2. In clinical practice
 - To identify patients in your practice who have negative symptoms and the severity of these symptoms
 - To monitor response of your patients to pharmacological and nonpharmacological interventions

TABLE 1-8 Scales used to assess negative symptoms

BPRS	Brief Psychiatric Rating Scale (retardation factor)
PANSS	Positive and Negative Syndrome Scale (negative symptom subscale; negative factor)
SANS	Scale for Assessment of Negative Symptoms
NSA-16	Negative Symptom Assessment
SDS	Schedule for the Deficit Syndrome

high-risk patients so that treatment can be initiated at the first signs of psychosis (Figure 1-4). Negative symptoms can also persist between psychotic episodes once schizophrenia has begun and reduce social and occupational functioning in the absence of positive symptoms.

Because of the increasing recognition of the importance of negative symptoms, their detection and treatment are now being emphasized. Despite the fact that our current antipsychotic drug treatments are limited in their ability to treat negative symptoms, psychosocial interventions along with antipsychotics can be helpful in reducing negative symptoms. There is even the possibility that instituting treatment for negative symptoms during the prodromal phase of schizophrenia may delay or prevent the onset of the illness, but this is still a matter of current research.

Beyond positive and negative symptoms of schizophrenia

Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness into five dimensions: not

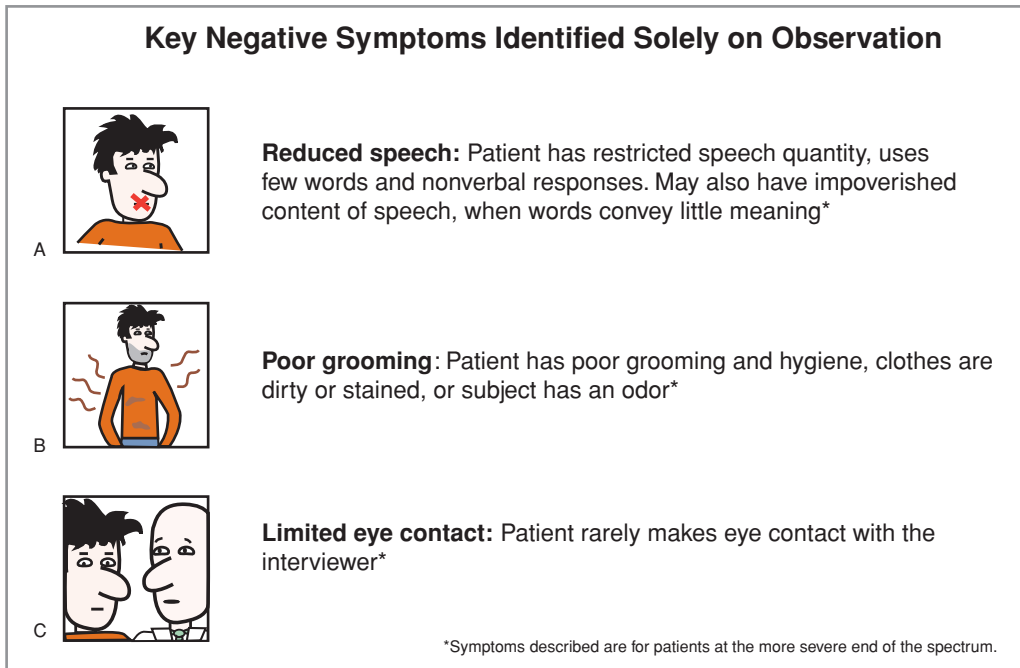


FIGURE 1-2 Negative symptoms identified by observation. Some negative symptoms of schizophrenia – such as reduced speech, poor grooming, and limited eye contact – can be identified solely by observing the patient.

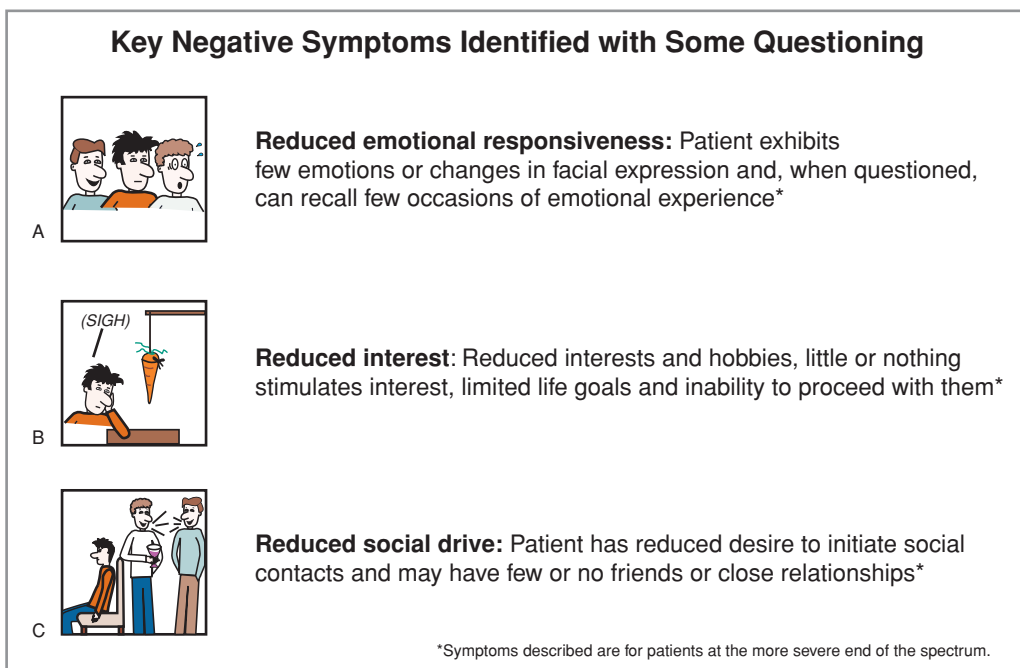


FIGURE 1-3 Negative symptoms identified by questioning. Other negative symptoms of schizophrenia can be identified by simple questioning. For example, brief questioning can reveal the degree of emotional responsiveness, interest level in hobbies or pursuing life goals, and desire to initiate and maintain social contacts.

TABLE 1-9 Selected items for rapid clinical assessment**1. Reduced range of emotions****Base rating on the subject's answers to the following queries:**

Have you felt anxious, nervous, or worried during the past week? What has that been like for you? What makes you feel this way? (Repeat for sad, happy, proud, scared, surprised, an angry)

During the last week, were there times when you felt numb or empty inside?

1. Normal range of emotion
2. Minimal reduction in range, may be extreme of normal
3. Range seems restricted relative to a normal person but subject convincingly reports at least four emotions
4. Subject convincingly identifies two or three emotional experiences
5. Subject can convincingly identify only one emotional experience
6. Subject reports little or no emotional range

Reduced range of emotion: Ask the patient whether he or she has experienced a range of emotions in the past week and rate according to the number of emotions described (Note that the ability to experience emotion is different from the ability to display affect)

2. Reduced interests**Base rating on assessment of range and intensity of subject's interests**

What do you enjoy doing? What else do you enjoy? Have you done these things in past week? Are you interested in what is going on in the world? Do you read the newspapers? Do you watch the news on TV? Can you tell me about some of the important news stories of the past week? Do you like sports? What is your favorite sport? Which is your favorite team? Who are the top players in this sport? Have you played in any sport during the past week?

1. Normal sense of purpose
2. Minimal reduction in purpose, may be extreme of normal
3. Life goals somewhat vague but current activities suggest purpose
4. Subject has difficulty coming up with life goals but activities are directed toward limited goal or goals
5. Goals are very limited or have to be suggested and activities are not focused toward achieving any of them
6. No identifiable life goals

Reduced Interests: Assess whether the patient has a normal range and intensity of interests

3. Reduced social drive**Rate based on patient responses to queries:**

Do you live alone or with someone else?

Do you like to be around other people? Do you spend much time with others?

Do you have difficulty feeling close to them?

How are your friends? How often do you see them? Did you see them this past week? Have you called them on the phone? When you got together this past week, who decided what to do and where to go?

Is anyone concerned about your happiness and well-being?

1. Normal social drive
2. Minimal reduction in social drive, may be extreme of normal
3. Desire for social interactions seems somewhat reduced
4. Obvious reduction in desire to initiate social contacts, but a number of contacts are initiated each week
5. Marked reduction in the subject's desire to initiate social contacts, but a few contacts are maintained at subject's initiation (as with family)
6. No desire to initiate any social interactions

Reduced social drive: Assess the level of social drive by probing the type of social interactions and their frequency. Remember to rate in reference to an age-matched normal.

(Cont.)

TABLE 1-9 (Cont.)

2. Restricted speech quantity**No specific question; rate based on observations during the interview.**

1. Normal speech quantity
2. Minimal reduction in quantity, may be extreme of normal
3. Speech quantity is reduced, but more obtained with minimal prodding
4. Flow of speech is maintained only by regularly prodding
5. Responses usually limited to a few words and/or detail is only obtained by prodding or bribing
6. Responses usually nonverbal or limited to one or two words despite efforts to elicit more

Restricted speech quantity: This item requires no specific questions and is rated based on observing the patient's speech during the interview.

All ratings should assess the function/behavior of the patient in reference to a normal age-matched person.

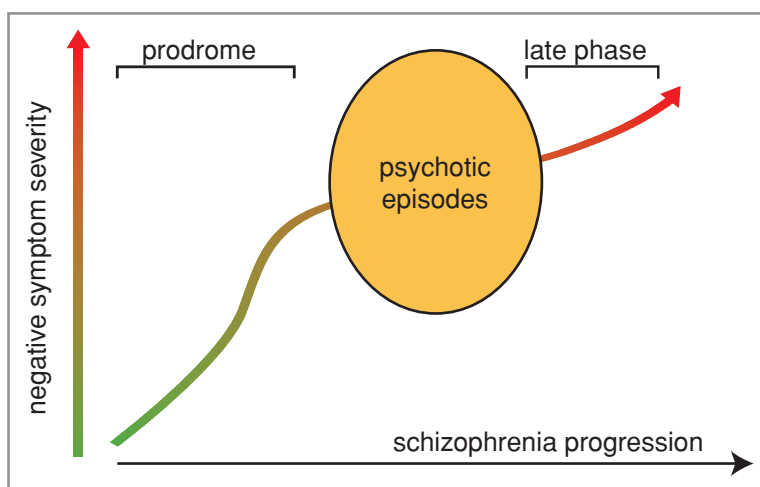


FIGURE 1-4 Negative symptoms in the prodromal phase. Negative symptoms of schizophrenia may occur during the prodromal phase, prior to developing the full syndrome of schizophrenia with both positive and negative symptoms. Theoretically, if such prodromal negative symptoms could be identified early and treated with psychosocial or pharmacological interventions prior to the onset of a psychotic break, it might be possible to delay or even prevent the onset of full-syndrome schizophrenia.

just positive and negative symptoms but also cognitive symptoms, aggressive symptoms, and affective symptoms (Figure 1-5). This is perhaps a more sophisticated if complicated manner of describing the symptoms of schizophrenia.

The overlaps among these five symptom dimensions are shown in Figure 1-6A, and some potentially overlapping symptoms are shown in Figure 1-6B. That is, aggressive symptoms such as assaultiveness, verbally abusive behaviors, and frank violence can occur with positive symptoms such as delusions and hallucinations, yet this is not always the case. It can be difficult to separate the symptoms of formal cognitive dysfunction and those of affective dysfunction from negative symptoms, as shown in Figure 1-6B. Since research is attempting to localize the specific areas of brain dysfunction for each of these