Positive vs. Negative Schizophrenia: A Critical Evaluation

by Nancy C. Andreasen

Abstract

Discussion of the positive vs. negative distinction often fails to address whether this distinction refers to symptoms, syndromes, or diseases. Symptoms and syndromes are etiologically nonspecific, while diseases have a specific identifiable pathophysiology or etiology. The positive vs. negative distinction is sometimes discussed as a hypothesis for identifying discrete subtypes of disease within the schizophrenic syndrome. In this overview, the evidence supporting this approach to subtyping is critically reviewed, and modifications of the original form of the hypothesis are proposed.

Most investigators concur that the illness we usually call by a single name—"schizophrenia"—is probably a heterogeneous group of disorders that share the common features of psychotic symptoms, partial response to neuroleptics, and a relatively poor outcome. Patients who share these common features are, however, clinically quite diverse. Further, research investigations have repeatedly demonstrated that the most consistent finding one can obtain is a very large variance in any variable that may be measured in schizophrenia, ranging from cognitive to neurochemical (Andreasen 1979; Weinberger et al. 1980; Crow et al. 1982*a*, 1982*b*). The diversity in schizophrenia suggests that the disorders grouped under this general term may in fact represent several different specific diseases that may differ in important ways, such as the involvement of different neurotransmitter systems, different brain regions, or different etiological agents.

The search for discrete subtypes of schizophrenia did not make much progress until relatively recently, when the distinction between positive and negative symptoms, originally proposed by Hughlings Jackson (1931), was revived (Fish 1962; Strauss, Carpenter, and Bartko 1974; Andreasen 1979*b*, 1982; Angrist, Rotrosen, and Gershon 1980; Crow 1980; Lewine, Fogg, and Meltzer 1983). Because the distinction has clear heuristic and theoretical appeal, many researchers throughout the world are actively studying this approach to subtyping schizophrenia. Much of the appeal of this distinction is based on the fact that it unites phenomenology, cognitive features, pharmacology, and pathophysiology into a single comprehensive hypothesis. It also clarifies issues by simplifying and polarizing them, thereby permitting scientific testing and study. An obvious weakness of the distinction, which is only a handicap if it is accepted uncritically or naively, is that it oversimplifies what is clearly a complex problem. This overview reviews some of the evidence supporting the positive vs. negative distinction, as well as some of the potential criticisms of it.

Positive (Type I, Florid) Schizophrenia

As proposed by Crow (1980), type I or positive schizophrenia is characterized phenomenologically by prominent positive symptoms such as delusions and hallucinations. Patients with this disorder may have a relatively acute onset, and the course of the illness is characterized by exacerbations and remissions. Many patients with prominent positive

Reprint requests should be sent to Dr. N.C. Andreasen, Dept. of Psychiatry, University of Iowa, 500 Newton Rd., Iowa City, IA 52242.

features have relatively normal premorbid functioning before the onset of their symptoms, and when the symptoms are in remission their social functioning may be relatively good.

Cognitive Features. The two-syndrome theory hypothesizes that the positive symptoms of schizophrenia are not due to any underlying structural brain abnormality and that patients with positive symptoms should, therefore, have normal cognitive function. Various studies of structural brain abnormalities that can be visualized using computed tomography (CT) have supported this theory (Johnstone et al. 1976; Crow 1980; Andreasen et al. 1982*b*). That is, in general, the various CT studies have not been able to document any relationship between positive symptoms and various indices of brain abnormality such as ventricular enlargement, sulcal enlargement, or cerebellar atrophy. A single exception is one study that reports ventricular enlargement in patients classified as paranoid subtype (Nasrallah et al. 1982). One study has shown that, if anything, patients with positive symptoms may tend to have relatively small ventricles (Andreasen et al. 1982*b*). A single informative case of a patient with persistent treatment-refractory delusions of a persecutory and sexual nature suggests that patients with positive symptoms may have structural abnormalities, but not of the type associated with atrophy. This particular patient had marked enlargement of the corpus callosum and the septal nuclei; one might hypothesize that she had a "hyperconnection" syndrome or excessive activation of the limbic system (Andreasen, unpublished data).

In addition to CT scanning, neuropsychological testing has also been used to explore the cognitive features of the positive vs. negative subtypes. As in the case of CT scanning, rather consistently patients with positive symptoms have been found to perform normally on various neuropsychological tests (Crow 1980; Andreasen et al. 1982*b*).

Pharmacologic Features. The florid symptoms of schizophrenia, such as delusions, hallucinations, or bizarre agitated behavior, tend to respond relatively well to neuroleptics. The mechanism of action of these neuroleptics is blockade of dopamine transmission. Other drugs that facilitate dopamine transmission, such as the amphetamines, are likely to exacerbate positive symptoms (Angrist, Rotrosen, and Gershon 1980). These pharmacological features implicate dopamine as an important mechanism in producing positive symptoms. Further, it has been frequently noted clinically that patients with prominent positive symptoms require relatively high doses of neuroleptics to diminish their positive symptoms, and that they have remarkably few side effects in spite of these high doses. The tolerance for high-dose neuroleptics further supports some neurochemical abnormality in positive schizophrenia. On the other hand, while positive symptoms may remit partially or fully with neuroleptic treatment, sometimes defect or negative symptoms persist after treatment.

Pathophysiology. The pathophysiology of positive symptoms is unknown, but the above pharmacological evidence suggests that the abnormality may reside at least in part in the dopamine system. The "dopamine hypothesis" proposes that the symptoms of schizophrenia are due to excessive dopamine transmission (Randrup and Munkvad 1965, 1966, 1972; Snyder, Greenberg, and Yamamura 1974; Seeman et al. 1976, 1984; Snyder 1976). The mechanism for this hyperdopaminergic transmission is unknown. Some evidence suggests that the abnormality may be in the receptor portion of the synapse (Snyder 1976). Crow et al. (1982*a*), using ^{3}H-spiroperidol in post-mortem brains, have noted increased numbers of D_2 receptors in the area of the nucleus accumbens. In a post-mortem brain study of neuropeptides, his team has also found increased vasoactive intestinal polypeptide (VIP) in the amygdala. Meltzer and colleagues have noted a relationship between low platelet monoamine oxidase (MAO) and high platelet 5-hydroxytryptamine (5HT) activity and positive symptoms (Meltzer et al. 1980; Jackman, Luchins, and Meltzer 1983). These latter findings suggest that other transmitters besides dopamine may be involved in producing positive symptoms. The platelet MAO and 5HT findings implicate serotonin, while the VIP findings suggest that acetyl choline could also be involved, since VIP and acetyl choline have been found to coexist and perhaps function as cotransmitters in autonomic ganglia (Krieger 1983). In any case, the underlying assumption concerning the pathophysiology of positive symptoms is that they are based primarily on a neurochemical rather than a structural abnormality. This hypothesis is supported in part by the mechanism of drug action and in part by the clinical observation that positive symptoms tend to be relatively reversible. The presumed area of abnormality is primarily subcortical, particularly temporolimbic.

Negative (Type II, Defect) Schizophrenia

The clinical features of negative schizophrenia tend to represent a mirror image to those of positive schizophrenia. The characteristic symptoms are negative or defect symptoms that represent a diminution of function rather than an excess. Typical negative symptoms include affective blunting, alogia (poverty of speech, poverty of content of speech), avolition and apathy, anhedonia and asociality, and attentional impairment. These symptoms usually begin insidiously without a clear onset, and patients therefore may have a long history of poor premorbid functioning. The course of the illness tends to be more chronic or deteriorating, and social functioning tends to be chronically impaired. Patients with prominent negative symptoms are often unable to hold a job and tend to remain socially isolated (Andreasen 1982*b*; Opler et al. 1984; Pearlson et al. 1984).

Cognitive Features. Brain-imaging techniques such as CT scanning have shown that schizophrenic patients in general have a higher rate of structural brain abnormalities than do control subjects (Johnstone et al. 1976; Weinberger et al. 1979*a*, 1980, 1981; Golden et al. 1980, 1981; Andreasen et al. 1982*c*; Nasrallah et al. 1982; Okasha and Madkour 1982; Reveley et al. 1982; Schulz et al. 1983). Studies that have focused on subtypes within the schizophrenia spectrum have noted that these structural brain abnormalities may occur more frequently in patients with prominent negative symptoms (Johnstone et al. 1976; Andreasen 1982*b*). The most common finding that has been noted is ventricular enlargement.

One study has also reported a relative increase in left-handedness among patients with prominent negative symptoms (Andreasen 1982*b*). This finding is important because it suggests something about the underlying mechanism that may lead to cerebral atrophy and cognitive impairment. Left-handedness may be either "genetic" or "pathological" (Satz 1972). Patients with genetic left-handedness tend to have a higher rate of left-handedness in other family members, while patients with pathological left-handedness develop it as a consequence of injury to their left hemisphere early in the developmental course (prenatally, perinatally, or within the first several years after birth). This injury to the left hemisphere produces a shift in the normal pattern of cerebral dominance. Normally the left hemisphere is used for the processing of fine motor activity and language. Because some injury has occurred to the left hemisphere early in life, however, patients with pathological left-handedness shift dominant processing to their uninjured right hemisphere, causing them to use the left hand for fine motor activity.

Patients with prominent negative symptoms also tend to have impaired performance on neuropsychological testing, using tests such as the Wechsler Adult Intelligence Scale (WAIS) (Rieder et al. 1979; Donnelly et al. 1980; Andreasen 1982*b*; Opler et al. 1984). While this impaired performance could be due to the inattention or lack of interest that characterize negative schizophrenia, it may also reflect actual cerebral injury. Patients with prominent negative symptoms tend to have a significantly lower educational achievement than do patients with prominent positive symptoms (Andreasen 1982*b*; Opler et al. 1984). Thus, there appears to be an association between the insidious onset of the illness, poor premorbid functioning, and cognitive impairment beginning early in life.

Pharmacological Features. Negative symptoms tend to respond less well to neuroleptic therapy than do positive symptoms. With aggressive treatment, hallucinations, positive thought disorder, and bizarre behavior can usually be markedly decreased in most patients. Delusions are frequently more treatment-refractory, but often respond as well. When these symptoms respond, the patient is sometimes left in a "defect state," characterized by alogia, avolition, and affective flattening. The picture is somewhat confused, however, by the fact that the extrapyramidal side effects of neuroleptics frequently produce a picture similar to affective flattening.

The observation that many patients with positive symptoms continue to have negative symptoms after treatment has led some clinicians to conclude that negative symptoms are more likely to be treatment-refractory (Johnstone et al. 1978). Further, some patients present with a clinical picture characterized primarily or predominantly by negative symptoms, with a relative paucity of positive symptoms. These patients, likewise, tend to show a relatively poor response to neuroleptic treatment. One study has shown an association between poor treatment response and ventricular enlargement, further supporting the argument for a "structural" and therefore "irreversible" abnormality underlying negative symptoms (Weinberger et al. 1980).

An alternate hypothesis for the pharmacology of negative symptoms has been proposed, however. This point of view argues that the

mechanisms underlying negative symptoms may also be neurochemical and therefore potentially reversible. For example, several investigators have proposed that negative symptoms may be due to a functional deficit in dopamine rather than an excess (Chouinard and Jones 1978; Lecrubier et al. 1980; Mackay 1980; Alpert and Friedhoff 1982). Such symptoms would, therefore, be more likely to respond to medications that facilitate or increase dopaminergic transmission, as neuroleptics have been reported to do in low doses (Puech, Simon, and Bossier 1978). Some investigators have experimented with the use of L-dopa (Buchanan et al. 1975; Gerlach and Lühdorf 1975; Inanaga et al. 1975). Others have proposed the use of "energizing" neuroleptics such as sulpiride (Lecrubier et al. 1980). Still other investigators have suggested that nonneuroleptic agents such as alprazolam may be useful in treating negative symptoms (Hollister, personal communication).

Pathophysiology. We know little that is definitive about the pathophysiology of negative symptoms, and as yet there is no widely accepted hypothesis similar to the dopamine hypothesis that can explain negative symptoms. The original explanation, proposed by Crow (1980), that negative symptoms are due to diffuse structural brain changes similar to those occurring in dementia appears to be an oversimplification. Not all patients with negative symptoms have ventricular enlargement or cortical atrophy, nor are negative symptoms consistently irreversible.

Reasoning a priori, one might argue that negative symptoms are most consistent with some type of frontal system disease. Patients who have experienced lesions in the prefrontal regions display symptoms remarkably similar to those that we have come to call negative symptoms: diminution in spontaneous movement and speech, loss of creativity, impaired attention and concentration, excessive concreteness, blunting of affect and emotional response, and profound apathy (Fuster 1980). One might argue simplistically that while positive symptoms might be due to a temporolimbic system abnormality, negative symptoms might be due to a frontal system abnormality. In fact, however, these two systems are interconnected through various major subcortical way-stations, such as the thalamus, and therefore subcortical dysfunction could explain both groups of symptoms.

The neurochemical mechanisms that might underlie negative schizophrenia are unclear. As described previously, some investigators have hypothesized that negative symptoms may reflect decreased dopaminergic transmission. This position has been argued from various vantage points by Lecrubier et al. (1980), Chouinard and Jones (1978), and Mackay (1980). Crow et al. (1982*a*) have shown that while the number of D_2 receptors is decreased in patients with positive symptoms, patients with negative symptoms have normal numbers of D_2 receptors, as measured in post-mortem brains. One problem with the hypodopaminergic theory of negative symptoms is that these symptoms sometimes coexist with positive symptoms in particular patients. While this theory can explain relatively "clean" instances of negative schizophrenia, it has more difficulty in accounting for the mixed patient.

Work in other centers has implicated the possible involvement of other transmitter systems. Lewine and Meltzer (1984) have observed an association between high platelet MAO and negative symptoms in male patients, thereby possibly implicating the serotonin system. Studying peptides, Ferrier et al. (in press) have observed decreased cholecystokinin (CCK) in the hippocampus and amygdala and somatostatin in the hippocampus of patients with prominent negative symptoms. If replicated, this finding would support a temporolimbic localization for negative symptoms as well. Further, since CCK and dopamine coexist in the midbrain as cotransmitters (Krieger 1983), this finding could provide further support for dopaminergic involvement.

The time may come soon when we can localize particular symptoms or syndromes of mental illness to transmitter or brain systems, but that time has not yet arrived. Attempting to localize these symptoms at present is like trying to solve a difficult and complex puzzle for which two or three pieces appear to be missing, lost, or unavailable.

Problems With the Positive vs. Negative Distinction

While theoretically appealing, and while supported by considerable evidence, the distinction between positive and negative schizophrenia just described nevertheless has a number of problems. It is best viewed as a heuristic approach to subtyping schizophrenia that lends itself to hypothesis testing and may be hypothesis generating. Investigators exploring this distinction must be aware of some of its conceptual and practical difficulties.

Failure to Distinguish Between Symptoms, Syndromes, and Diseases. The literature on the

positive vs. negative distinction is often marred by a failure to recognize this basic distinction, which is fundamental to understanding phenomenology, diagnosis, and classification.

Symptoms (as well as signs) are the clinical features of illness; they may occur in many different disorders (e.g., delusions). Symptoms can be added up as a continuous measure and used to identify or define a syndrome and evaluate its severity.

Syndromes are a set of clinical features that tend to occur together (e.g., dementia). Syndromes are phenomenologically similar, but may differ in etiology (e.g., multi-infarct dementia vs. Alzheimer's dementia).

Diseases are discrete illnesses that differ in their pathophysiology or etiology (e.g., multiple sclerosis, neurosyphilis).

Since symptoms are relatively nonspecific, their presence does not necessarily have any predictive power. For example, the presence of a single negative symptom, or even several, does not necessarily indicate that a person has schizophrenia, nor does the presence of one or several positive symptoms. Depressed patients may have apathy or impaired attention, and they may also have delusions or hallucinations. To say that a symptom is nonspecific, however, is not to say that it is unimportant. Symptoms are the fundamental material with which diagnosticians and psychometricians must work.

Yet another problem that has not been adequately addressed is *how* to decide that a symptom is positive or negative. In most early work, the decision was simply made a priori. For some symptoms, this decision, based on "face validity," makes good sense. Items on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) such as emotional withdrawal and blunted affect are rather clear negative symptoms, as are items on the Krawiecki scale (Krawiecki, Goldberg, and Vaughan 1977) such as affective flattening or poverty of speech. On the other hand, incongruity of affect moves back and forth from one study to another as a positive or negative symptom, and the place of psychomotor retardation or catatonic motor symptoms is also unclear. More work needs to be done on these symptoms, both through various measures of internal consistency and through determining their predictive power in relation to various external validators.

Symptoms can be rated either categorically or continuously; that is, they can either be scored as present vs. absent, or they can be rated by overall severity. The scales developed by Lewine, Fogg, and Meltzer (1983) based on the Rasch model use the former approach, while the Krawiecka scale and the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) of Andreasen (1982*a*, 1984) use the latter approach. Scales that ask for a rating of present vs. absent may be simpler to use, although it is frequently difficult to identify the threshold for deciding that a symptom is present, particularly in the case of negative symptoms. On the other hand, scales that use continuous measures, such as the SANS and the SAPS, lend themselves well to dimensional analyses that explore correlations.

As anyone with the most rudimentary knowledge of statistics is aware, however, the study of correlations permits only limited inferences. Correlations indicate the relationship between variables, but they do not permit one to draw any conclusions about causality. Ultimately, our goal is to determine the causes of psychiatric disorders, and the examination of correlations is only a first approximation to that goal. Although that fact is really quite rudimentary, all of us occasionally show some "cognitive slippage" in our eagerness to make inferences about relationships and assume that finding a correlation may help explain etiology.

If one wishes to attempt to identify either diseases or discrete subtypes of diseases, then one must posit a categorical approach. Instead of examining the relationship between symptoms and other variables, one must divide patients into groups and study some relevant correlate. Patients can be divided into groups on the basis of phenomenology (e.g., those with prominent negative symptoms and those who lack prominent negative symptoms), or they can be divided on the basis of some biological variable (e.g., those with high or normal numbers of D_2 receptors, or those with high vs. low platelet MAO). To speak of a disease or a subtype of disease implies that one is studying a phenomenon that is discontinuous from normality or that two subtypes of a disorder are discontinuous from one another.

Inadequately Developed Definitions of Symptoms. When interest in the positive vs. negative distinction was reawakened, investigators had few instruments at hand with which to measure negative symptoms. These symptoms had been in disfavor because of a frequently expressed concern that they could not be rated reliably. Initially, scales such as the Krawiecki or BPRS were used because they were the only ones available. The negative symptoms measured by these scales are

relatively limited, and their psychometric properties with respect to the positive vs. negative distinction have not been adequately investigated. Unfortunately, however, much of the research described above is based on the use of these scales.

More recently, several new scales have been developed, such as the SANS, the SAPS, and the Lewine Scale. The SANS describes five major groups of negative symptoms (alogia, affective flattening, avolition-apathy, anhedonia-asociality, and attentional impairment). It has well-documented reliability and some external validity, such as correlation with premorbid functioning, ventricle-brain ratio, and cognitive impairment. The scale has good internal consistency. The SAPS, which is designed to provide similar measurements of relevant positive symptoms, is also available. These scales lend themselves well to repeated measures designs. The Lewine scale is derived from the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) (Honigfeld et al. 1966). It also has good reliability. These two scales provide a much fuller description of the range of positive and negative symptoms than do those used previously.

Inadequately Developed Definitions of Syndromes and Diseases. While the two scales described above provide some relatively standard and comprehensive ways of measuring positive and negative symptoms, at present there are few well-conceptualized ways of defining positive and negative schizophrenia as a syndrome or disease. One set of criteria for defining positive, negative, and mixed schizophrenia has been proposed, and these criteria appear to have some predictive validity (Andreasen 1982*b*). Independent studies in other centers have also applied these criteria and found them to be valid and useful (Dion and Dellario 1985). One alternate approach is to classify patients as negative if they show *any* negative symptoms; this approach is based on the underlying assumption that negative symptoms must represent some type of "defect" that is of more theoretical significance than positive symptoms. Alternatively, one can add up scale scores on the various positive and negative symptom scales currently available and identify patients at extreme ends of the positive vs. negative continuum; this approach is clearly more syndromal in its orientation. Given our current state of knowledge, no method of defining patients as negative or positive can be considered preeminent. This is clearly an area where further investigation is needed.

Failure to Deal With the "Mixed" Patient. Early formulations of the positive vs. negative distinction failed to discuss the issue of the "mixed" patient. Positive and negative symptoms were treated as if they were distinct entities, and the fact that positive and negative symptoms frequently co-occur in a single patient was ignored. While it is possible that positive and negative schizophrenia are indeed two distinct disease entities with differing underlying pathophysiology or etiology or alternatively that they are syndromes at opposite ends of a continuum, in real life they are also groups of symptoms that may overlap in a single patient. If one speaks about positive vs. negative schizophrenia categorically, then how is one to explain the coexistence of positive and negative symptoms within a single patient?

Several explanations are possible. One is that while "pure negative" schizophrenia and "pure positive" schizophrenia may be distinct subtypes, patients with mixed symptoms represent yet another subtype, or even several different subtypes. A second possible explanation is that patients with mixed positive and negative symptoms are at an intermediate stage in the course of the illness; this hypothesis assumes that some patients may eventually evolve from a positive state to a negative state, and that the negative state represents the true or underlying disorder. Thus patients who are mixed are in fact negative, but the predominantly negative syndrome has not yet developed. A third explanation might be that the symptoms of schizophrenia could be due to multiple causes, and that some of these causes coexist in some patients; for example, patients with a mixture of positive and negative symptoms might represent those patients who have both suffered perinatal cerebral injury (producing atrophic damage and negative symptoms) and also suffer from a genetic tendency toward hyperdopaminergic transmission (leading to positive symptoms).

Yet another possible explanation is that there may be a single causative agent that affects different brain regions; for example, a slow virus might lead to patchy damage in different regions, and those patients who have a predominantly prefrontal lesion would have negative symptoms, while those with a predominantly temporolimbic localization would have positive symptoms, while some patients might have involvement in both areas. Yet another explanation might be that multiple neurochemical systems are involved in the production of the

symptoms of schizophrenia, leading to various kinds of imbalance; for example, an excess of dopamine might lead to positive symptoms, an excess of γ-aminobutyric acid or serotonin might lead to negative symptoms, and a mixture of symptoms could be due to an imbalance of multiple systems. Some of these explanations are obviously theoretical or even a bit fanciful, but they serve to suggest that a single simple theoretical model will probably not be able to explain the symptoms, course, and classification of schizophrenia. A complex interactive model involving both environment and genetics, the involvement of multiple neurotransmitter systems, and the involvement of multiple brain regions is required.

Failure to Take Longitudinal Course Into Account. While the positive vs. negative distinction introduces some course variables into the model, such as poor premorbid functioning or poor outcome, it does not recognize the fact that the phenomenology of schizophrenia may vary dramatically over time. As described above, some patients with positive symptoms develop a defect state after the positive symptoms remit. Others clearly have a lifetime longitudinal course beginning with florid symptoms and later leading to deterioration. Some patients may begin with predominantly negative symptoms and remain in that state throughout their lives. To date, we have had relatively few studies on the longitudinal course of positive and negative symptoms over time. Work by Pfohl and Winokur (1982, 1983) indicates that the symptoms of schizophrenia do indeed vary. They studied a cohort of 52 chronic schizophrenic patients who were institutionalized before the era of antipsychotic medications and noted that during a 25-year period hallucinations and delusions became less frequent, while negative symptoms such as avolition, impaired social interaction, and affective flattening became more frequent. Thus, it appears that some schizophrenic patients do evolve from a positive to a negative state. Since the patients in this study were all institutionalized, it is not clear whether these findings are generalizable to patients with a less severe syndrome. Clearly, more longitudinal studies of the course of positive vs. negative symptoms are needed.

Conclusion

Schizophrenia may represent a single illness, or it may be a heterogeneous group of disorders referred to by a single name. If the latter is the case, and if research investigations fail to recognize the heterogeneity of the disorder and pool together unlike patients, then positive results will be lost because they are averaged out in a diverse sample. The large variance noted in most studies of schizophrenia supports this latter possibility. Consequently, efforts to identify discrete subtypes are of great importance.

The positive vs. negative approach to subtyping schizophrenia has recently aroused considerable interest, primarily because it synthesizes in a single theory many disparate observations and also makes "good clinical sense." In addition, it generates a number of scientifically interesting and testable hypotheses. One must add that like many useful theories (ranging from the catecholamine hypothesis through the Oedipus complex to negative cognitive sets), it represents an oversimplification. The tendency to oversimplify is both its strength and its weakness. We can use this approach best by recognizing that it is perhaps overly simplistic, but that it therefore permits the study of rather complex issues if applied intelligently and with caution.

The positive vs. negative distinction warrants much additional future study. Possible future directions include genetic and family studies to explore the prevalence and pattern of symptoms within families, detailed examination of the course of symptoms over time, application of new brain imaging technology to assist in the localization of positive vs. negative symptoms, attempts to define in more detail the brain regions and neurochemical systems involved, and detailed examination of pharmacological response with variable dose strategies and various types of medication.

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The Author

Nancy C. Andreasen, M.D., Ph.D., is Professor of Psychiatry, The University of Iowa, Iowa City, IA.

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