Progress in the Study of Negative Symptoms

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A selective review of the negative symptoms of schizophrenia is an appropriate article to result from the festschrift honoring William T. Carpenter Jr, as he has made substantial contributions in this area. This review assesses progress in 3 areas in which he has been an important investigator: the distinction between primary vs secondary negative symptoms; the appropriate design for treatment trials; and the nosology of negative symptoms.

Key words: festschrift/factor analysis/Carpenter/negative symptoms/deficit/randomized clinical trials/nosology

Negative symptoms account for a substantial part of the impairment suffered by people with schizophrenia and have long been a focus of research on schizophrenia. Recognizable descriptions of the negative symptoms of schizophrenia can be found as early as the mid-1800s, with Wilhelm Griesinger’s descriptions of an “absence of will,” followed by Kraepelin’s description of a “weakening of….the mainsprings of volition” among some people with schizophrenia. A landmark development in the scientific study of negative symptoms was the publication of the Brief Psychiatric Rating Scale in 1962, which has been cited more than 7500 times in the world literature and included negative symptom items. The Scale for the Assessment of Negative Symptoms brought further attention to negative symptoms as a separate area of research and, potentially, a separate therapeutic target and greatly facilitated progress in the study of negative symptoms.

The present review of recent developments in the concept of negative symptoms grew out of a presentation at the festschrift for William T. Carpenter Jr, held in June 2013. It reviews areas of research on negative symptoms in which he has made important contributions: the nosology of negative symptoms; the distinction between primary vs secondary symptoms; and the appropriate design for negative symptom treatment trials.

Nosology

In 1974, Carpenter and coworkers proposed separating, for research purposes, 3 groups of symptoms within schizophrenia: positive symptoms, negative symptoms, and problems in interpersonal relationships. On the basis of the many factor analytic studies of the psychopathology of schizophrenia that appeared after that proposal, Buchanan and Carpenter subsequently outlined a research strategy that distinguished among positive symptoms, negative symptoms, and disorganization. In this approach, one would, by testing many individual hypotheses, test the overarching hypothesis that these domains have distinctive risk factors, course, treatment response, and biological correlates. This “domains of psychopathology” strategy led to a proposal for a default analysis of studies of schizophrenia.

In 2005 Carpenter cochaired the Consensus Development Conference on Negative Symptoms sponsored by the US National Institute of Mental Health. The Conference resulted in a recommendation that a new instrument for quantifying negative symptoms be developed. Two instruments grew out of that recommendation: the Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS). At the Consensus Development Conference, a review of the factor analytic studies of the Scale for the Assessment of Negative Symptoms was presented. In those studies, 2 factors were found with some consistency (sometimes, additional factors were found as well); an expressivity factor consisting of blunted affect and aloxia, and a factor that combines anhedonia, avolition, and asociality. Subsequently, very similar factors were found using the BNSS, the Schedule for the Deficit Syndrome, and the CAINS. Of the 2 new scales that implement the recommendations of the Consensus Development Conference—the BNSS and CAINS—the BNSS has so far had somewhat stronger item loading for a crisper separation of the 2 factors. One study found good stability of these factors at 5-year follow-up. The negative
symptom items on the Positive and Negative Syndrome Scale does not appear to yield these 2 factors consistently.\textsuperscript{19}

The significance of these factors is not yet clear; to date, there are relatively few studies of their correlates. However, the avolition factor may be a stronger prediction of overall function than is the expressivity factor,\textsuperscript{16,20} and the 2 factors may differ in their response to certain treatments.\textsuperscript{21} In principle, rapid progress on understanding the significance of these 2 factors should be possible, because an analysis of the correlates of expressivity vs avolition/anhedonia is possible in most studies of negative symptoms.

Primary vs Secondary Symptoms
In 1988, Carpenter and coworkers\textsuperscript{22} argued that it is important to distinguish negative symptoms that are secondary to factors such as depression, a suspicious withdrawal, overwhelming psychotic symptoms, and extrapyramidal side effects from those symptoms that cannot be attributed to such factors. They termed symptoms that could not be attributed to these other factors—and therefore are due to the disease itself—primary symptoms, in contrast to symptoms secondary to these factors. They argued that people with schizophrenia who have enduring, primary symptoms were more likely to comprise a meaningful subtype than a negative symptom subtype that included patients with both primary and secondary symptoms.

Carpenter et al\textsuperscript{22} proposed diagnostic criteria to distinguish deficit patients—those with primary, enduring negative symptoms—from nondeficit patients, who do not have such symptoms. The Maryland group subsequently published a refined version of the diagnostic criteria as well as a manual for making this distinction.\textsuperscript{14} The same group of investigators later used the term deficit schizophrenia to refer to schizophrenia with primary, enduring negative symptoms, in contrast to nondeficit schizophrenia, in which any negative symptoms are considered secondary.\textsuperscript{23} The Maryland group demonstrated strong reliability for this categorization,\textsuperscript{14} but there remained a question whether other researchers could also do so. Reports of good inter-rater agreement in other research groups soon followed, as did evidence of the stability of the diagnosis.\textsuperscript{24,25}

The present brief review of the validity of the deficit/nondeficit categorization is organized into 5 dimensions that distinguish diseases: signs and symptoms, course of illness, etiological and risk factors, biological correlates, and treatment response. More detailed reviews of deficit/nondeficit differences have been published.\textsuperscript{23,26}

Signs and Symptoms
There are symptomatic differences between the 2 groups in addition to those used to make the diagnosis. Deficit patients have less awareness of their impairments, including dyskinetic movements,\textsuperscript{27,28} as well as less anxiety and depression. The anxiety and depression differences are stable,\textsuperscript{1,29} and the lesser severity of these symptoms in the deficit group contrasts with their poorer social function and greater social isolation.\textsuperscript{24} The 2 groups do not differ on psychotic symptoms: hallucinations, delusions, and disorganized thought and behavior. However, deficit patients’ lack of social drive extends to the content of their delusions, because they have less severe delusions with an exclusively social content.\textsuperscript{30} Deficit patients also have a greater risk of dyskinetic movements than do nondeficit patients, a difference that is not confounded by differences in treatment history.\textsuperscript{31,32}

Course of Illness
Deficit patients have, on average, greater social dysfunction prior to the onset of psychosis than do nondeficit patients.\textsuperscript{33} In contrast to what one might expect in a group with poorer social function, deficit patients have on average less severe drug abuse.\textsuperscript{34} Deficit patients also have poorer outcome on follow-up, as shown in 2 separate studies (1 from Italy) with 5 years of follow-up, and 1 with an average follow-up of 19 years.\textsuperscript{1,16,24} Despite their poorer function but consistent with their less severe depression and poorer insight, deficit patients less frequently have suicidal thoughts and may have less risk of suicide.\textsuperscript{24}

Etiological and Risk Factors
An association between deficit schizophrenia and summer birth has been found in studies from 6 countries\textsuperscript{35} but may not exist in lower latitudes.\textsuperscript{36} The combination of a replicated summer birth association for deficit schizophrenia, and an association with winter for schizophrenia as a whole—ie, both deficit and nondeficit groups—suggests that winter birth is a risk factor for nondeficit schizophrenia alone. Compared with nondeficit probands, patients with deficit schizophrenia have a higher prevalence of psychosis among their relatives.\textsuperscript{37,38} The nonpsychotic relatives of deficit probands also have a greater prevalence of deficit-like features than do the relatives of nondeficit probands,\textsuperscript{38} and within schizophrenia, there is a significant sibling concordance for the deficit/nondeficit categorization.\textsuperscript{39} Antibodies to cytomegalovirus but not other herpes viruses were found to be more prevalent in people with deficit compared with nondeficit schizophrenia.\textsuperscript{40}

Biological Correlates
The deficit and nondeficit groups differ on several biological correlates.

Imaging
Deficit/nondeficit differences have been found in studies of structural, functional, and neurochemical imaging. Arango et al\textsuperscript{41} found that male deficit patients had significantly larger ventricles than nonpatient control subjects, but there was no difference between control subjects
and either male nondeficit patients or female patients. Fischer et al.\(^4\) found smaller gray matter volumes in deficit patients, compared with both nondiagnosis and control subjects, in the superior prefrontal, superior temporal, and middle temporal gyri. There was no difference in any of several subcortical areas. Voinoskos and coworkers\(^4\) found a difference between deficit and nondiagnosis groups in white matter integrity as measured by diffusion tensor imaging. The difference was widespread; there were some suggestions that the difference was particularly large in the right arcuate, left uncinate, and right inferior longitudinal fasciculi. These bundles extend to many anatomical areas. In the same study, there was no difference in cortical thickness, but the deficit sample was relatively small.

Tammenga et al.\(^4\) found decreased activation in deficit compared with both nondiagnosis and control subjects in the thalamus, as well as in frontal and parietal cortex. Other functional differences have also been found: increased activation in the left amygdala of deficit patients in response to an emotional facial recognition task, which the investigators interpreted as due to an abnormality in habituation\(^4\); and, using memory tasks, less activation in the frontal cortex in deficit compared with nondiagnosis patients.

A neurochemical imaging study of deficit and nondiagnosis patients found a lower N-acetylaspartate/creatine (NAC) ratio in the prefrontal cortex of deficit patients compared with nondiagnosis and control subjects, a difference the investigators suggested reflected a loss of neurons in the prefrontal cortex of deficit patients.\(^4\) The same group subsequently found NAC levels were correlated with Stroop scores in deficit but not nondiagnosis patients or control subjects, suggesting a relationship between poor right medial prefrontal cortex function and poor selective attention exists only in deficit patients.\(^4\)

Taken together, the imaging studies suggest deficit/nondiagnosis differences are widespread, and the differences do not appear to be present solely in either gray or white matter.\(^5\)

**Metabolic Differences.** In a study of newly diagnosed, antipsychotic-naive patients, both deficit and nondiagnosis subjects had abnormal glucose tolerance compared with matched controls subjects. However, the deficit patients had significantly less severe glucose intolerance than did nondiagnosis patients. In contrast, although deficit patients had abnormally high interleukin-6 concentrations compared with control subjects, nondiagnosis patients did not differ from control subjects and had significantly lower concentrations than deficit patients.\(^4\)\(^5\)

**Neurocognitive Measures.** In a meta-analysis, deficit patients were found to have greater cognitive impairment than nondiagnosis patients, with a pattern that was not consistent with a discrete anatomical distribution.\(^5\) In a study in which deficit patients had significantly poorer performance on the continuous performance test (CPT) and span of apprehension tasks than nondiagnosis patients, the nondiagnosis group did not differ from control subjects on the CPT, but were significantly impaired compared with control subjects on the span of apprehension task.\(^6\)

Mucci and coworkers\(^5\) found a double dissociation in event-related potentials. Deficit but not nondiagnosis patients differed from control subjects on N1 amplitude and current source density, while nondiagnosis but not deficit patients differed from control subjects on P3 measures. The 2 patient groups also differed from each other on these measures. In contrast, deficit and nondiagnosis groups were found not to differ on P50 gating with an auditory stimulus.\(^5\)

Deficit patients have a significantly greater impairment in smell identification than nondiagnosis patients; this relationship is correlated with a measure of their asociality but is not due to differences in intelligence quotient.\(^5\)\(^6\) Deficit patients also rate pleasant smells as less pleasant than do nondiagnosis patients.\(^6\)

In a study of neurological signs, deficit patients had greater impairment than nondiagnosis patients in sensory integration, but the groups did not differ on other groups of neurological signs, or on total neurological impairment.\(^6\)

**Treatment Response**

There is no evidence that there is a difference between deficit and nondiagnosis patients in terms of the response of their positive psychotic symptoms to antipsychotics. However, preliminary studies of both psychosocial and pharmacological treatments suggest that some treatment that are effective for the negative symptoms of nondiagnosis patients are less effective, or ineffective, among deficit patients.\(^6\)\(^6\)

**Summary**

This review of deficit/nondeficit differences suggests that the deficit group constitutes a separate disease within the syndrome of schizophrenia. These differences are not confounded by deficit/nondeficit differences in demographic features, antipsychotic treatment, or the severity of psychotic symptoms or drug abuse. Some correlates of primary, enduring negative symptoms differ from those of negative symptoms more broadly defined.\(^1\)\(^3\)\(^7\) Several findings refute the interpretation that the deficit group simply has a more severe form of the same etiopathophysiology as nondiagnosis schizophrenia, including the deficit group’s decreased drug abuse, less severe depression and parasuicidal behavior, summer rather than winter birth, and double dissociations in metabolic and event-related potential measures.

Imaging studies and the meta-analysis of neuropsychological studies, taken together, are consistent with the view that people with deficit schizophrenia have a pathophysiological process that affects many areas in the brain. This
view is consistent with the increased density of interstitial cells of the white matter in deficit subjects, compared with nondeficit schizophrenia subjects and nonpatient control subjects, that has been found in both the dorsolateral prefrontal cortex and inferior parietal cortex. The abnormality in this cell population further suggests that there is a deficit/nondeficit difference in neuronal migration during gestation and that this difference is the basis of the clinical differences. It is intriguing to speculate that this abnormal migration in the deficit group is related to one or more of the risk factors associated with deficit but not nondeficit schizophrenia. However, while the summer birth effect and a different familial risk have been replicated, the cytomegalovirus difference—which might lend itself to animal studies—has not.

**Treatment Trials of Negative Symptoms**

Demonstration of the validity of the primary/secondary distinction provided a basis for a proposed study design for treatment trials focused on negative symptoms. In this approach, only patients with stable and moderate to severe negative symptoms, but with minimal positive symptoms and depression, would be enrolled in such a trial. This design provides a method for dealing with the problem that arises in interpreting treatment studies: if both negative symptoms and positive psychotic symptoms improve, the negative symptom improvement may be due to an improvement in secondary negative symptoms only. This design has subsequently been adopted by academic and industry investigators, and it was endorsed by the Consensus Development Conference cochaired by Dr. Carpenter.

**Discussion**

Negative symptoms constitute one of the most impairing aspects of schizophrenia, and to date, treatments for these problems have been very disappointing. Recent treatment studies and greater understanding of the biological underpinnings of negative symptoms raise the hope that this situation will change. Through his work, William T. Carpenter Jr has contributed greatly to this progress.

**Acknowledgment**

The author has declared that there are no conflicts of interest in relation to the subject of this study.

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