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Primary, Enduring Negative Symptoms: An Update on Research

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We previously proposed that people with schizophrenia who have primary, enduring negative symptoms have a disease—deficit schizophrenia (DS)—that is separate from that affecting people with schizophrenia without these features. Additional evidence consistent with the separate disease hypothesis has accumulated in recent years. White matter changes may be widespread in deficit compared to nondeficit patients and may relate to problems in early brain migration. These 2 patient groups also appear to differ on metabolic measures prior to antipsychotic treatment. Studies of reward and defeatist beliefs provide the basis for future treatment trials. The 2 factors or groups within negative symptoms broadly defined (both primary and secondary) have also been found in DS, and recent evidence suggests these 2 symptom groups have different correlates and reflect the existence of 2 groups with in DS. Negative symptoms are found in disorders other than schizophrenia, and excess summer birth, a deficit risk factor, has been found in a nonpatient group with deficit-like features. It may be useful in future research to determine whether findings in DS extend to patients with other neuropsychiatric disorders who also have negative symptoms.

Key words: deficit schizophrenia/nosology/negative symptoms/psychopathology/schizophrenia

In a review published in 2001, we first suggested that patients with primary, enduring negative symptoms have a disease that is separate from that found in other patients with schizophrenia, which we called deficit schizophrenia (DS).[1] Secondary negative symptoms are those caused by other factors, such as medication side effects, depression, or psychotic symptoms; symptoms that are not attributable to such factors are considered primary or idiopathic. Deficit patients and those without such symptoms (nondeficit patients [ND]) differ on 5 dimensions used to distinguish diseases: signs and symptoms, the course of illness, treatment response, biological correlates, and risk/etiological factors. These differences could not be attributed to confounding by the duration of illness, antipsychotic treatment, the severity of positive psychotic symptoms, or depression. Some findings were not consistent with the interpretation that deficit patients simply had a more severe form of the same illness, as the 2 groups exhibited a double dissociation with regard to some variables, and in ways, the deficit group was less severely affected.

In 2008 we provided an update on research in this area.[2] Since that review, there have been changes in the concept of negative symptoms, both primary and secondary, as well as exciting new evidence on the distinctive features of DS.

Are We Talking About the Same Thing?

We previously noted[1] that different research groups have sometimes published contradictory results on DS/ND differences, but an examination of the clinical characteristics of the 2 groups revealed that the researchers had not made similar categorizations. There are 2 tools for categorizing subjects into DS and ND groups: the Schedule for the Deficit Syndrome (SDS)[3] and the Proxy for the Deficit Syndrome (PDS).[4] Each method has advantages and disadvantages. The SDS should typically have a larger effect size than the PDS. The disadvantage is that it is time-consuming to administer, and required training is also time-consuming. The advantages of the PDS are that it can often be applied to existing datasets in which the SDS was not used, and a large number of patients can be categorized at once. To implement a PDS, measures of emotionality (depression the most important measure, but anxiety, guilt, and hostility are helpful) and

the severity of negative symptoms are needed. The disadvantages of the PDS are (1) the complexity of testing the validity of the categorization and the selection of cutoff points, (2) probably at least 75 subjects are required for it to work well, and (3) the effect sizes are likely to be less for the PDS than for the SDS, as the PDS is likely to have some miscategorizations compared to the SDS lead standard.

Even when researchers develop good interrater reliability for the SDS within their research groups, the problem of reliability between different groups of researchers is more difficult, and the use of the SDS or PDS does not avoid this problem completely. Usually, the problem with intergroup reliability is distinguishing primary vs secondary negative symptoms. Because of the problem with intergroup reliability, for both the SDS and the PDS, it would be helpful to provide detailed clinical comparisons of the deficit and nondeficit groups in publications.

Signs and Symptoms

Specific negative symptoms play an important part in the criteria for DS, but other symptom differences compared to NS were previously noted.[1,2]

Negative Symptom Factors

Studies of negative symptom rating scales (the Scale for the Assessment of Negative Symptoms [SANS], the Brief Negative Symptom Scale [BNSS], and the Clinical Assessment Interview for Negative Symptoms [CAINS]) in DS and ND combined have typically found 2 factors, consisting of diminished expressivity (blunted affect and poverty of speech; ED) and avolition/anhedonia/asociality (AAA).[5–7] Studies of the SDS, including 3 in DS only,[8–13] found a 2-factor solution very similar to that found in negative symptom rating scales. The SDS factor structure showed longitudinal stability over 1- and 5-year periods.[10,12]

The SDS factor structure differs from that of the negative symptom rating scales as the SDS diminished emotional range item, which has no exact counterpart in the rating scales, loads with DE, and the SDS has no anhedonia items. The SDS avolition factor has shown a strong correlation with an index of intrinsic motivation and with a deficit of striatal activation during reward anticipation.[14] These correlations are similar to the ones reported for the avolition factor of the BNSS[15] and provide an external validation of the construct of avolition as a deficit of motivation.[16]

In an Italian study, AAA factor scores from the SDS had a stronger association with psychosocial functioning than the DS/ND categorization, while ED factor scores showed a stronger association with poor insight concerning the need for treatment and community activities than the DS/ND categorization.[10] Strauss et al[11] classified DS patients (using cluster analysis) into High-AAA and High-ED subgroups. AAA compared to ED patients were more frequently males, more frequently had a family history of psychotic disorders and an insidious illness onset, and had more severe thought disorder, worse premorbid social adjustment, and occupational functioning. These studies of the 2 factors within DS are intriguing, as the 2 factors may reflect the existence of 2 groups of patients who might differ with regard to risk factors, function, pathophysiology, and treatment response. The PDS has usually used blunted affect alone as the measure of negative symptoms, which might impact the relative prevalence of and EE groups when the PDS is used; however, the emotionality measure appears to account for most of the agreement with SDS categorizations.[4]

Other Signs and Symptoms

Using taxometrics, Ahmed et al[17] found 2 groups based on SDS negative symptom scores, with substantial agreement between the DS/ND categorizations made with the SDS and assignment to the 2 taxa ($\kappa = .795$, $P < .0001$). Taxometrics yielded a larger negative symptom group than the one delineated by the SDS, with 28% vs 20% of the sample placed in a negative symptom group by these methods, respectively. The taxometric classification had stronger relationships to summer birth, male sex, premorbid adjustment, neurocognition, and psychosocial functioning than did the SDS diagnosis. However, within the taxon, SDS negative symptom severity scores were significantly related to premorbid adjustment, cognitive impairment, and psychosocial function. Blanchard et al[18] previously found a negative symptom taxon with a prevalence of 28%–36%; that study and the study of Ahmed and coworkers provides evidence for the predictive validity of the DS/ND categorization but raise the question of whether the criteria may be more restrictive than is ideal.

Mechanistic models of negative symptoms have been proposed that integrate neurobiology, neurocognition, and psychology; one model can be found in the article by Strauss & Cohen in this issue. Defeatist attitudes are a component of recent models and are proposed to mediate the relationship between neurocognitive dysfunction and negative symptoms, including those of DS patients.[19–21] This relationship suggests psychological treatments for defeatist attitudes may decrease negative symptoms, but it has not always been found.[22] Moreover, a meta-analysis[23] found a small effect size for the association between defeatist beliefs and negative symptoms ($r = .24$, $P < .001$).

Trotman et al[24] found a greater decrease in awareness of impairment in DS than in ND patients, consistent with earlier reports of decreased awareness of dyskinetic movements[25] and cognitive impairment.[26] Dantas et al[27] and Pegoraro et al[28] did not find any significant difference in the

Schedule for the Assessment of Insight—Expanded Version between DS and ND, when controlling for cognitive impairment. However, a reduced awareness of impairment on all dimensions of the Scale for the Unawareness of Mental Disorders was reported by Galderisi et al[10] in DS vs ND after controlling for differences in cognitive abilities. Whether the discrepancies are due to the different instruments used to assess insight, or to differences in the prevalence of AAA vs ED patients, is unclear; as noted above, the expressivity factor impairments but not those of the anhedonia/avolition/asociality factor may contribute to the reduction of insight.

Course of Illness

Premorbid Adjustment

As previously reported,[2] premorbid adjustment is worse in DS than in ND patients, particularly in the earliest epochs of life (from childhood to adolescence); recent studies have confirmed this difference. Strauss et al[29] investigated premorbid adjustment in academic and social domains and the pattern of deterioration of functioning from early to late adolescence. Both DS and ND patients showed impaired and deteriorating academic functioning, a pattern generally observed in schizophrenia, but the DS group showed a more severe impairment and deterioration in the social domain. A study of first-episode patients[12] confirmed a greater impairment in premorbid functioning and a greater deterioration of functioning in DS vs ND. Bucci et al,[30] assessing function up to the age of 11 years, found that DS patients had greater social withdrawal than their healthy siblings and ND patients, and worse social and academic premorbid adjustment than ND.

Stability of Deficit Features and Relationship to Function

The DS/ND categorization was previously noted to be stable over time, and DS consistently associated with a more severe course and worse functional outcome.[2] Follow-up studies have reported longitudinal stability ranging from 67% to 87%[10,12,31]; all found a lower rate of remission and poor functional outcome in DS compared to ND.[10,12,31] No study is available on the different stability of the AAA and EE domains within DS samples.

Biological Correlates

Neurocognitive Correlates

Most cognition studies subsequent to our previous review[2] have confirmed a generalized cognitive impairment in DS vs both ND and controls.[10,32,33]

Some recent studies investigated performance on neuropsychological measures of emotion processing, learning from feedback, and effort-based decision making, cognitive domains which might be more relevant to the pathophysiology of DS than is a generalized cognitive impairment. Strauss et al[34] examined the performance on the Attention Grabbing task, a test of automatic attentional bias for emotional stimuli, and the Lingering effect, a measure of disengagement from these stimuli. DS patients showed less bias for positive emotional stimuli, unlike healthy controls and ND patients, as well as difficulty in disengaging from negative stimuli (suggesting cognitive inflexibility.) The severity of the SDS measure of diminished emotional range, which has loaded with ED-like items on factor analysis, correlated with reduced bias to both positive and negative emotions, and with the difficulty in disengaging from negative stimuli. Anhedonia was associated only with the reduced bias for positive emotions. Strauss et al[35] also found DS patients had a complex pattern of differences from ND patients with regard to ratings of smells, which seemed to reflect abnormal processing of pleasant odors, paralleling the abnormality in their earlier study. Fervaha et al[36] used an effort-based decision-making task and found that DS subjects gave less effort to obtain a reward than ND, a finding that was not confounded by the severity of negative symptoms or lower general cognitive abilities in DS. The relevance of these new findings to avolition remains to be assessed. Vogel et al[37] investigated learning from feedback (in particular negative feedback) using the first 4 trials of the Wisconsin Card Sorting Test. DS patients did not learn from feedback. Their difficulty was associated with AAA but not with ED, depression/anxiety, or positive psychotic symptoms. Although there was a negative correlation of learning performance with chlorpromazine equivalent dose, the 2 patient groups did not differ in mean daily chlorpromazine dose, suggesting that dose could not explain the group difference in learning from feedback.

Electrophysiological Correlates

A few electrophysiological investigations have been published since 2008. Early event-related potential components, such as P50, did not differ between DS and ND,[38,39] while later components showed a double dissociation of findings in DS and ND.[39] In particular, Li et al[39] reported that: (1) the post-imperative negative variation (PINV) latency was prolonged in ND and shortened in DS; (2) P300 latency was prolonged only in ND, and (3) the contingent negative variation (CNV) expectancy wave was delayed only in DS. A study investigating the association of DS with abnormalities of eye movement initiation[40] did not confirm the previously reported significant association with DS.[41] Overall, these studies have used heterogeneous paradigms and indices, and suffer from small sample sizes and a lack of replication.

Neurological Correlates

A higher frequency of neurological abnormalities, including neurological soft signs, parkinsonism, and dyskinesia, was previously reported in DS vs ND patients.[2]

Telfer et al[42] reported a significant association between DS and tardive dyskinesia in patients with schizophrenia treated with antipsychotics. The chlorpromazine dose did not differ between DS and ND, and tremor and rigidity were more frequent in ND, so confounding by antipsychotic treatment seems unlikely. Peralta et al[12] included drug-naïve patients and reported impairment in motor sequencing, in agreement with previous findings,[43] and a greater severity of parkinsonism, dyskinesia, and catatonia in DS than in ND subjects.

Brain Imaging

Studies by 4 different research groups have found abnormalities in the white matter of DS compared to ND patients[44–47]; usually the DS group has been more abnormal than ND patients. Spalletta et al[46] found a complex pattern of differences among the 2 patient groups and control subjects, including double dissociations for DS and ND, although they also shared some abnormalities (perhaps related to psychosis). Replication of this pattern would be important evidence for the separate disease hypothesis.

The white matter findings, if replicated, may relate to earlier postmortem studies that found an increase in the density of interstitial cells of the white matter (ICWMs) in DS compared to both ND and control subjects in the dorsolateral prefrontal and parietal cortex.[48,49] ICWMs are neurons that appear to be part of a population of cells that do not migrate as far from the neural plate as is normal. While these postmortem studies included small numbers of subjects, and we are not aware of a replication, these imaging and postmortem studies raise the question of whether the distinctive clinical features of DS may arise from abnormal development and function of the white matter. Whether there is a relationship between these white matter findings and reported abnormalities in frontoparietal and frontotemporal coupling—defined as correlations of regional cortical thickness—in DS compared to ND patients[50] is not clear.

There are also recent findings on gray matter volume (GMV). In a study of the cerebellum, DS patients had a greater GMV reduction in the culmen than did ND patients.[51] The first degree relatives of DS but not ND patients had a volume reduction in the same region. Another study found smaller GMV in the superior prefrontal as well as superior and middle temporal gyri in DS patients than in ND patients or control subjects.[52] Takayanagi et al[53] found the anterior cingulate cortex in deficit patients to be thinner in DS than ND patients. Cascella et al[54] found several cortical and subcortical regional volume decreases in DS compared to ND patients, particularly in regions related to emotion processing (insula, amygdala, medial prefrontal and temporal lobe structures), goal-directed behavior (putamen, Brodmann area 6), and attention (precuneus and superior temporal gyrus). Other gray matter decreases were reported previously.[1,2] Fernandez-Egea et al[55] found increased activation of the left amygdala in DS compared to ND patients in a facial recognition task. The volume of the nucleus accumbens was also found to be decreased in DS compared to NS.[56]

Both the gray and white matter studies have been limited by small sample sizes, which may account for the differences in findings across studies. However, there appears to be a general trend for smaller regional volumes and more anisotropy in DS compared to NS. Multicenter studies or meta-analyses would be helpful in this area.

Metabolic Measures

In antipsychotic-naïve patients, DS but not ND patients had higher concentrations of interleukin-6 and C-reactive protein than control subjects; the larger, ND group did not differ from control subjects.[57] However, while both DS and ND patients, compared to matched control subjects, had abnormal glucose tolerance in a glucose tolerance test, the ND group had significantly higher values than the DS group.[58] These results constitute a double dissociation in glucose intolerance and inflammation: the DS group had greater inflammation but less severe glucose intolerance than ND patients. However, in a sample consisting mainly of chronically ill subjects, DS patients had a higher risk of cardiovascular events than did ND patients.[59] The findings in the antipsychotic-naïve and chronically ill patients both need replication; survival bias may contribute to this discrepancy.

Risk/Etiological Factors

Previously noted, replicated risk factors for DS are: (1) male gender; (2) a family history of schizophrenia, and (3) an excess of summer births (unlike schizophrenia as a whole, which is associated with a winter birth excess).[2] Kirkpatrick et al[60] also found an association between summer birth and deficit-like features in a nonpatient population. No genetic risk factor has consistently been found in association with DS.[61]

Treatment Response

Despite the importance of the topic, we have not found any treatment trials of DS patients since our last review. There have been pharmaceutical trials that have adopted the recommended design for the study of negative symptoms,[62] and the results of 2 such industry trials[63,64] suggest there was an effect on primary negative symptoms, but these findings would need replication and further clarification. The defeatist attitudes work suggests cognitive behavioral therapy might improve negative symptoms should treatment decrease these attitudes.

Discussion

Since our last review, promising but preliminary results have come from studies of white matter, metabolic abnormalities, abnormalities in reward, and defeatist beliefs. However, an important weakness of this literature is the lack of attempted replications of many of the most interesting findings. The summer birth association is the most important exception, with multiple replications.[65]

The 2 factors—AAA and DE—that have been found in both negative symptoms broadly defined (ie, both primary and secondary symptoms), as well as in DS patients alone, complicate the interpretation of existing data on DS/ND differences. These factors have been differentially related to a variety of outcome measures,[10,11,66] as well as to differences in imaging correlates.[14–16] The results of Strauss et al[11] in 2 large samples suggest that these 2 factors reflect the existence of separate groups of patients, including separate groups within DS. To what extent do these symptom groups differ in their correlates, including risk factors, pathophysiology, and treatment response? In other words, to what extent is DS a heterogeneous syndrome, consisting of AAA and DE patients? These findings raise another possibility: some of the discrepancies in the DS/ND literature are due to differences in the proportions of the AAA and DE groups from study to study. The strategy used by Strauss and coworkers of sorting deficit patients into these 2 groups, when the sample size is sufficiently large, would be an appropriate tool for asking this question. Three studies[10,11,17] further suggest that combining dimensional and categorical approaches in the same study may be a powerful approach.

Several findings suggest very early life events are major contributors to the etiology of deficit features. The studies of premorbid function referenced in this article and in our earlier reviews have detected behavioral abnormalities earlier in life in DS compared to ND patients. The preliminary evidence on the abnormal placement of the interstitial cells of the white matter, which probably has a prenatal origin, is also consistent with abnormalities in very early development. These findings further suggest the metabolic findings found in antipsychotic-naïve patients with deficit features may reflect prenatal metabolic programming. The summer birth association is also consistent with a very early origin of DS features; whether the DS and ND groups differ with regard to early life risk factors other than summer birth, such as prenatal stress and childhood adverse events, is not known.

It is not clear which of the many recent findings on negative symptoms broadly defined—ie, including both primary and secondary symptoms—apply to deficit patients. For instance, a zinc transporter molecule variant has been found in schizophrenia patients who on average have marked negative symptoms and poor cognition.[67] This might be a gene for DS, but only if the negative symptoms of patients with this variant are primary rather than secondary.

Strauss and Cohen discuss negative symptoms across diagnoses in this issue. Should firmer evidence on the pathophysiology of primary negative symptoms be found, this could provide the basis for hypothesis testing in other disorders in which negative symptoms are found, such as traumatic brain injury, dementia, and depression. However, in preliminary studies, patients with traumatic brain injury had negative symptoms that resembled those of patients with schizophrenia,[68] but hippocampal volume had a (negative) correlation with apathy in patients with traumatic brain injury, but not in patients with schizophrenia.[69]

The work on defeatist attitudes is an important reminder of the need for biopsychosocial models. Research in some other neuropsychiatric disorders, most notably in depression, has shown that the combination of biological and psychological treatments is the most powerful approach for patients. It seems increasingly likely that this will be the case for deficit features as well. Patients with DS also appear to have both an abnormal hedonic response and cognitive impairment, suggesting another possible combination of treatment targets to improve negative symptoms.

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