Avolition, Negative Symptoms, and a Clinical Science Journey and Transition to the Future

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Introduction

The concept of schizophrenia as a disease entity was dominant during the twentieth century. Once tertiary syphilis was identified as causative of "insanity," Kraepelin (1919) was able to parse two other major mental illnesses based on prognosis, course, and manifest pathology. But even as he established the dichotomy of the major psychoses, he recognized distinctive pathological processes within dementia praecox. The dissociative pathology described by Bleuler (1911) was combined with "the weakening of the wellsprings of volition," the latter leading to emotional dullness, lack of occupation, and drive. In short, negative symptoms combined with dissociative pathology and poor prognosis defined the disorder that Bleuler (1911) named schizophrenia. This gave emphasis to dissociative pathology as primary and fundamental in each case, thereby cementing the concept of a disease entity where all cases shared the essential pathology. Bleuler (1911) also gave emphasis to other domains of pathology that he considered primary, including the affective pathology that we now include in the negative symptom complex.

While schizophrenia was considered a disease with all cases having the fundamental pathology, Bleuler's (1911) suggestion of the group of schizophrenias and his designation of four primary psychopathologies (i.e., autism, ambivalence, affect, and associative pathology) opened the door to heterogeneity and perhaps implied a

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clinical syndrome rather than a disease entity. During the middle of the twentieth century, the field produced splitters such as Leonhard and Kleist, with up to 50 subtypes, and lumpers such as Schneider and Langfeld, who could distinguish true from pseudo-schizophrenia based on selected symptoms considered unique in identifying true schizophrenia in the absence of delirium. This latter view was already influential in Europe when DSM-III enshrined even a single Schneiderian first-rank symptom as sufficient for a diagnosis of schizophrenia and omitted negative symptom pathology from the symptom criteria for a diagnosis. This shift away from avolition, associative pathology, and interpersonal pathology to a reality distortion, or ego boundary disturbance of first-rank symptoms, may have addressed the perceived overdiagnosis of schizophrenia in the USA. But the narrow versus broad concept of schizophrenia had not been settled at the level of validation, and family pedigree studies of that time implicated genetics in the etiology of schizophrenia, and broad definitions provided more power in these studies. It is interesting to note that current GWAS and polygenic score analyses confirm a genetic risk cutting across diagnostic boundaries.

By the 1970s, it was evident that schizophrenia was not, and, perhaps, could not be, validated as a disease entity. Individual patients varied in presenting symptoms, developmental history, treatment response, family history, degree of cognitive impairment, presence of neurological soft signs and psychomotor abnormalities, and social and occupational function. With DSM-III, it was clear that patients could meet criteria for schizophrenia without having any symptoms in common. One patient may have thought disorder and psychomotor abnormalities, while another may meet criteria based on a single Schneiderian first-rank symptom. There is no evidence that all cases share a defining etiopathophysiology. Nonetheless, most research in the remainder of the twentieth century and to the present time is designed with schizophrenia as the independent variable. Even in the area of genetics, schizophrenia remains a phenotype in GWAS studies and in the creation of polygenic scores. But viewing schizophrenia as a clinical syndrome where deconstruction is essential for many scientific and clinical purposes has been proposed for over 40 years (Strauss, Carpenter, & Bartko, 1974) and has recently become prominent with the NIMH MATRICS, Cogs, BSNIP and RDoC initiatives (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml), and cross-cutting dimensions included in section 3 of the DSM-5. The following discussion is focused on negative symptoms and their application in syndrome deconstruction.

The Negative Symptom Construct

Kraepelin is the critical starting point with his separation of the avolitional pathology from dissociative pathology. To quote Kraepelin (1919):

> *Now if we make a general survey of the psychic clinical picture of dementia praecox… there are apparently two principal groups of disorders which characterize the malady. On the one hand we observe a weakening of those emotional activities which permanently form the*

> *mainsprings of volition… The result of this part of the morbid process is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and of ability for independent action. The essence of personality is thereby destroyed, the best and most precious parts of its being, as Griesinger once expressed it, torn from her. With the annihilation of personal will, the possibility of further development is lost, which is dependent wholly on the activity of volition.*

Inherent in this quote from Kraepelin is an assumption that affective deficits are core to volitional impairment. This view stood for a substantial period of time, and in mid-century, two theorists are important in advancing these notions. Rado focused on anhedonia, viewed it as closely linked to the genetics of schizophrenia, and understood the pathology as based on diminished experience of pleasure from positive stimuli. Meehl, in a theoretical proposal still influential, viewed anhedonia as a defining and genetic-based feature of schizotaxia forming the vulnerability for schizotypy and schizophrenia. To elaborate on this, Meehl conceptualized schizotaxia, the overarching category of which schizophrenia and schizotypy are a part, as a basic pathophysiology stemming from a pervasive neural defect (or, in other words, an underlying genetic predisposition) (Meehl, 1962). This pathophysiology combines with social factors to cause the formation of schizotypy, a personality disorder, while a small percentage convert to schizophrenia. While in his original conceptualization of this conversion, Meehl cited the change as being mainly reliant upon family dynamics (in particular the "schizophrenogenic mother") (Meehl, 1962), he later revised his theory based on clinical observations (Meehl, 1989). In this later conceptualization, Meehl observed that those patients who later converted to schizophrenia appeared to experience less pleasure in childhood, the forerunner of the negative symptom of anhedonia (Meehl, 1989). Therefore, Meehl's concept placed what is now termed negative symptom pathology in a genetic and developmental framework and as psychopathology at the core of schizophrenia.

Overall, these pioneers influenced clinical concepts, and the view that persons with schizophrenia have reduced drive based on anhedonia has only recently been challenged (Barch & Dowd, 2010; Gard, Kring, Gard, Horan, & Green, 2007; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Kring & Barch, 2014; Kring & Moran, 2008; Strauss, Waltz, & Gold, 2014). A common experience for the clinician is a patient with schizophrenia who had diminished motivation. The person may express interest in activities, and pleasure in common positive experiences, but fails to initiate these activities and participates in a passive manner. Modern conceptualizations hold that this deficit may result from a series of reward processing abnormalities that prevent normal hedonic experiences from translating into motivated behavior (Strauss et al., 2014).

Negative and positive symptom terminology was introduced in 1974 (Strauss et al., 1974). The terms were drawn from Hughlings Jackson's neurology, where negative referred to the loss of function as a direct result of a lesion and positive represented disinhibition of action as a secondary consequence of the lesion. Strauss et al. (1974) made explicit that the application in schizophrenia was to distinguish diminished or loss of normal function from distorted or excessive manifestations of normal function. These were viewed as separate domains of pathology with negative

Table 1 Different models of schizophrenia

Model	Authors	Components
Tripartite model	Strauss et al. (1974)	– Positive
		– Negative
		– Interpersonal
3-Component	Liddle (1987) and Bilder et al. (1985)	– Positive
	Andreasen & Olsen (1982)	– Negative
		– Disorganization
4-Component	Peralta and Cuesta (1994)	– Reality distortion
		– Disorganization
		– Negative symptoms
		– Interpersonal pathology

symptoms such as restricted affect and low motivation, and positive symptoms such as disorders of form or content of speech and thought. Psychomotor disturbances, poor insight, and disorders observed in interpersonal relating were also defined. Based on experience in the IPSS, these six psychopathology domains were identified and then collapsed into three categories: positive psychotic symptoms, negative symptoms, and pathology best observed in the interpersonal context. This 1974 tripartite model was later modified by (Andreasen & Olsen, 1982), Liddle (1987), and Bilder, Mukherjee, Rieder, and Pandurangi (1985), each separating thought disorder from delusions and hallucinations and each dropping the interpersonal pathology. Peralta and Cuesta (1994) tested models in their large and carefully evaluated cohort and determined that one and two component models failed to account for the observed pathology. The two three-component models fit the data better, and the strongest model was a four-component model: reality distortion, disorganization, negative symptoms, and interpersonal pathology. The three- and four-component models are an attempt to integrate the divergent types of psychopathology into a coherent concept of schizophrenia without implying uniform etiology or pathophysiology (Table 1).

Other approaches with the negative symptom concept have been more robust in advancing knowledge. Negative symptoms can be used to define a subgroup of patients reducing syndrome heterogeneity. This has been done with Crow's type I and type II model (Crow, 1985) and Andreasen's positive versus negative model (Andreasen & Olsen, 1982).

Most recently, the deficit schizophrenia versus non-deficit schizophrenia model has received extensive investigation and is a putative disease entity within the schizophrenia syndrome (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001; Kirkpatrick & Galderisi, 2008). However, the most robust approach involves separating domains of pathology (Buchanan & Gold, 1996; Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990; Strauss et al., 1974) to identify psychopathology targets for etiology, pathophysiology, and therapeutic discovery. Here the negative symptom construct is a domain of pathology to be considered as a separate dimension. The remainder of this manuscript will describe issues relating to a negative

symptom dimension and segue to Part II by Strauss et al. in this volume, where current laboratory research is clarifying fundamental issues related to negative symptoms.

Primary vs. Secondary Negative Symptoms and "Deficit Schizophrenia"

Several factors influenced the formation of the deficit schizophrenia line of inquiry. Negative symptom pathology stood in clear distinction from positive psychotic symptoms. Within subject correlation was low, negative symptoms were often absent in persons meeting diagnostic criteria for schizophrenia, and negative symptoms, in contrast to positive symptoms, appeared to be more broadly predictive of course, more robustly related to function, and often appeared well in advance of psychosis, perhaps marking the developmental pathology associated with some forms of schizophrenia. But these observations were present when methodology required a clinical judgment as to whether the negative symptoms were primary to schizophrenia or secondary to other causal pathways associated with schizophrenia but not core pathology. Commonly used rating scales did not require this differential judgment. In most studies, negative symptom ratings might be the consequence of drugs that impair energy or mute affect, or asociality may be the result of paranoid guardedness, or failure to engage in social and occupational activities may be related to preoccupation with voices, or a protective withdrawal from demanding interpersonal interactions may relate to sensory overload or cognitive challenge. The separation of primary from secondary negative symptoms was central to understanding psychopathology (Carpenter, Heinrichs, & Wagman, 1988), but most studies accept negative symptom ratings without this differential. This problem was initially addressed with two assessment methods: the Quality of Life Scale (Heinrichs, Hanlon, & Carpenter, 1984) with seven putative primary negative symptoms and the Schedule for the Deficit Syndrome (Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989) that explicitly separated primary from secondary negative symptoms. That this separation is important seems self-evident, and several studies have documented that key findings require this differentiation (Kirkpatrick et al., 2001; Kirkpatrick, Fernandez-Egea, Garcia-Rizo, & Bernardo, 2009; Kopelowicz, Zarate, Tripodis, Gonzalez, & Mintz, 2000). The Quality of Life Scale is the standard in the field for assessment of outcome (Harvey et al., 2011), and the SDS was the only explicit approach to defining the deficit schizophrenia subgroup based on primary negative symptoms.

Isolating patients with schizophrenia who had primary negative symptoms provided several approaches to the acquisition of new knowledge. First, the subgroup with primary negative symptoms may represent Kraepelin's original concept in the context of a much broader definition of schizophrenia based on positive psychotic symptoms. Hence, studies contrasting deficit with non-deficit schizophrenia would test for critical differences. Indeed, many of the confounds that plague

schizophrenia research including antipsychotic drug exposure could be balanced between deficit and non-deficit subgroups permitting strong inference research (Carpenter, Buchanan, Kirkpatrick, Tamminga, & Wood, 1993). Deficit schizophrenia appears to be the only validated subtype and traditional subtypes have been dropped from DSM-5.

Second, the deficit categorization has led to several breakthroughs in understanding the etiology of negative symptoms that are core aspects of the disease process itself, rather than secondary to factors such as depression, anxiety, psychosis, and disorganization. For example, compared to non-deficit patients, those with deficit schizophrenia have a distinct pattern of premorbid function characterized by progressive social decline. Course differs, with a more insidious onset for deficit patients that persists into the chronic phase of illness and limits rates of recovery. There has been a greater association with summer birth, whereas winter birth is more common in non-deficit schizophrenia. Prevalence is much higher in men than women. Deficit patients are at reduced risk for some psychiatric symptoms associated with heightened emotional response, such as suicidality, posttraumatic stress disorder, depression, and substance use disorders. Deficit patients have more neurological soft signs, distinct structural and functional brain abnormalities, more severe neurocognitive impairment, and emotional information processing deficits characterized by impaired processing of positive stimuli. A summary of differences between deficit and non-deficit schizophrenia can be found in Table 2.

Finally, the deficit concept has important implications for study design. Primary negative symptoms could be the specific target of investigation rather than a subgroup marker. Here the paradigm shift is away from disorder or disorder subtype classification to deconstructed domains of pathology (Carpenter & Buchanan, 1989; Strauss et al., 1974). It is critical to have an operational definition of these domains in order to facilitate instrument assessment for research and practice, particularly in terms of the development of clinical trials, as treating the negative symptoms of schizophrenia is an unmet need (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). As such, interest has recently turned to methods of identifying and investigating these domains specifically as a means of encouraging treatment development (Kirkpatrick et al., 2006).

Special Issues Relating to Negative Symptom Therapeutics

Whether there is efficacious therapy for negative symptoms has been controversial. The issue is partially resolved with the primary/secondary distinction. This has been clarified with a treatment algorithm (Carpenter, Heinrichs, & Alphs, 1985) for identifying cause and treatment for secondary negative symptoms. For example, apathy may be caused by a sedating drug, restricted expression of emotion in the face may be drug-induced akinesia, social withdrawal may be based on paranoia, diminished anticipation of pleasure may be secondary to depression, and so forth. Secondary sources need to be excluded in order to focus on negative symptoms that are core

Table 2 Differences between deficit and non-deficit SZ

Domain	Key findings
Risk factors/etiology	• Family pedigree studies with a deficit schizophrenia proband are associated with increased rates of schizophrenia among relatives, increased likelihood of being the deficit form, and increased social isolation in the absence of psychosis compared with family pedigrees with a non-deficit schizophrenia proband (Dollfus, Ribeyre, & Petit, 1996; Kirkpatrick, Ross, et al., 2000; Ross et al., 2000)
	• Val158Met of catechol-*O*-methyl transferase (COMT) and the *2236T>C allele polymorphism of the dihydropyrimidinase-related protein 2 (DRP-2) gene may be associated with deficit but not nondeficit schizophrenia (Galderisi et al., 2005; Hong et al., 2005)
	• No association between COMT Val158Met polymorphism and deficit classification (Wonodi et al., 2006)
	• The T393C polymorphism of the GNAS1 gene is associated with deficit schizophrenia but not the nondeficit subtype (Minoretti et al., 2006)
	• Two latent class analyses of genetic data produced a "deficit subgroup" (Fanous et al., 2008; Holliday, McLean, Nyholt, & Mowry, 2009)
	• Association between summer birth (June–August) and deficit status in the northern hemisphere (Kirkpatrick et al., 2001)
	• No association with summer birth has been replicated in the southern hemisphere (McGrath & Welham, 1999; Welham et al., 2006)
	• Men have a greater likelihood of the deficit syndrome than women (Roy, Maziade, Labbé, & Mérette, 2001)
Symptoms	• Deficit patients may demonstrate more severe negative and disorganization symptoms than nondeficit patients (Cohen, Brown, & Minor, 2010; Kirkpatrick et al., 2001)
	• Deficit patients may endorse fewer mood symptoms including suicidal ideation, paranoid ideation, hostility, and substance use behaviors as well as symptoms of PTSD (Cohen et al., 2010; Kirkpatrick et al., 2001; Strauss et al., 2011)
	• Deficit and nondeficit patients are comparable in the severity of positive symptoms (Cohen et al., 2010; Kirkpatrick et al., 2001)

(continued)

Table 2 (continued)

Domain	Key findings
Course and treatment response	• Deficit patients may be more psychosocially impaired in childhood and adolescence before the first episode, independent of the degree of positive, negative, or mood symptoms (Peralta et al., 2014; Strauss et al., 2012)
	• Deficit patients demonstrate greater premorbid deterioration and a longer duration of untreated illness than nondeficit patients (Peralta et al., 2014)
	• Deficit syndrome patients have lower rates of recovery (Strauss, Harrow, et al., 2010)
	• Insidious onset with stable course in deficit schizophrenia and negative symptoms are present at onset (Fenton & McGlashan, 1994)
	• Deficit schizophrenia is associated with poorer psychosocial outcomes at long-term follow-up relative to nondeficit schizophrenia (Chemerinski, Reichenberg, Kirkpatrick, Bowie, & Harvey, 2006; Tek, Kirkpatrick, & Buchanan, 2001)
	• Whereas negative symptoms in nondeficit patients may be responsive to antipsychotic treatment (e.g., olanzapine or clozapine treatment), negative symptoms in deficit schizophrenia are more treatment refractory (Kopelowicz et al., 2000; Lindenmayer, Khan, Iskander, Abad, & Parker, 2007)
Neurological abnormalities	• More severe neurological impairment in deficit schizophrenia (Arango, Kirkpatrick, & Buchanan, 2000; Peralta et al., 2014)
	• Evidence of both quantitative (Benoit, Bodnar, Malla, Joober, & Lepage, 2012; Voineskos et al., 2013; Volpe, Mucci, Quarantelli, Galderisi, & Maj, 2012) and qualitative differences in neurological deficits (Benoit et al., 2012; Mucci et al., 2007; Peralta et al., 2014; Turetsky et al., 1995)
	• Deficit patients demonstrate more severe abnormal movements and neurological soft signs than nondeficit patients (Peralta et al., 2014)

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Table 2 (continued)

Domain	Key findings
Specific neuropathology	• Deficit patients demonstrate greater gray matter reductions in right frontal medial-orbital gyrus and the right parahippocampal gyrus relative to nondeficit patients (Benoit et al., 2012)
	• Deficit patients demonstrate reductions in cortical thickness and specific white matter tract abnormalities in the right inferior longitudinal fasciculus, right arcuate fasciculus, and left uncinate fasciculus (Voineskos et al., 2013)
	• Deficit patients demonstrate greater reductions in their superior and middle temporal gyri relative to nondeficit patients (Fischer et al., 2012)
	• Deficit patients demonstrate reductions in regional cerebral blood flow (rCBF) in their right orbitofrontal region relative to nondeficit patients (Kanahara et al., 2013)
	• Deficit and nondeficit patients show differential patterns of event-related potential (ERP) activation deficits (Li et al., 2015; Mucci et al., 2007)
	• Deficit syndrome patients show stronger frontoparietal and frontotemporal coupling than nondeficit (Wheeler et al., 2015)
	• Deficit patients demonstrated impairments in N1 activation in their posterior cingulate and parahippocampal gyrus; nondeficit patients demonstrated impairments in P3 activation bilateral cingulate, left superior, and left middle frontal areas (Mucci et al., 2007)
	• Deficit patients demonstrate low activation in the middle frontal cortex and inferior parietal cortex (Lahti et al., 2001)
	• Deficit patients differ from nondeficit patients in patterns of DTI white matter diffusivity decrease and increase (Spalletta et al., 2015)
	• Deficit patients show stronger frontoparietal and frontotemporal coupling than nondeficit patients (Wheeler et al., 2015)
Neurocognition	• Deficit and nondeficit patients demonstrate both severity and qualitative differences in their neurocognitive profiles (Cohen et al., 2007; Dantas, Barros, Fernandes, Li, & Banzato, 2011; Wang, Yao, Kirkpatrick, Shi, & Yi, 2008)
	• Deficit patients demonstrate greater impairments in executive functioning, processing speed, attention, complex motor sequencing, social cognition, olfaction, and language (Chen et al., 2014; Cohen et al., 2007; Dantas et al., 2011; Strauss et al., 2008; Strauss, Allen, et al., 2010; Strauss, Jetha, et al., 2010; Wang et al., 2008)
	• Deficit patients show differences in emotion processing, specifically that deficit patients have poorer processing of positive emotion (Strauss et al., 2008; Strauss, Allen, et al., 2010; Strauss, Jetha, et al., 2010)

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Table 2 (continued)

Domain	Key findings
Other findings	• *MIR137* gene: There is evidence that deficit syndrome patients have a specific variation of *MIR137* gene (Lett et al., 2013)
	• *Cytomegalovirus seropositivity*: Association between deficit status and antibody cytomegalovirus seropositivity (Dickerson et al., 2006)
	• *Glucose tolerance*: higher 2-h glucose concentrations in individuals with nondeficit schizophrenia compared to deficit individuals and healthy controls in a glucose tolerance test (Dickerson et al., 2006; Kirkpatrick et al., 2009)
	• *Neuroinflammation*: higher C-reactive protein levels in individuals with deficit than nondeficit schizophrenia (Garcia-Rizo et al., 2012)
	• Plasma cortisol levels: individuals with deficit schizophrenia have significantly lower levels of plasma cortisol than nondeficit schizophrenia (White et al., 2014)

Note: Table expanded from Ahmed et al. (2015)

features of schizophrenia pathology. However, this is rarely done and meta-analyses of negative symptom clinical trials are extensively based on secondary negative symptoms (Fusar-Poli et al., 2015). Negative symptom ratings routinely improve in clinical trials where positive symptoms improve, but this is not proof of efficacy. The FDA refers to this as pseudo-specificity. The MATRICS Conference reached a consensus on the trial design on which efficacy claims could be based (Kirkpatrick et al., 2006). This design, first presented by Kirkpatrick, Kopelowicz, Buchanan, and Carpenter (2000) and used in the CONSIST study (Buchanan et al., 2007), essentially requires persistent negative symptoms at baseline and a trial design that minimizes and/or holds constant secondary sources of negative symptoms. In head-to-head comparison of antipsychotic drugs, it has also been important to remember that many of these drugs induce negative symptoms. If drug A beats drug B on negative symptoms, it may be because drug A is more benign rather than more efficacious. This is important clinically, but is not proof of efficacy.

The new scales, described below, have greater construct validity but do not eliminate the confound from secondary sources. However, persistent negative symptoms are an important clinical problem whether or not they can be established as primary. The case for selecting persistent rather than primary for most clinical trials has been made. This, combined with the paradigmatic clinical trial design, addresses a major clinical issue and the following assessment instruments are well suited for application. Etiology research will still need a method to identify primary negative symptoms. The issue of treatment response of negative symptoms has been addressed in a meta-analysis including all types of therapies which found only very modest responsiveness probably attributed to secondary negative symptom improvement (Fusar-Poli et al., 2015).

Negative Symptom Assessment

Structured clinical interviews and rating scales such as the Brief Psychiatric Rating Scale (BPRS) have always contained items related to negative symptom pathology, but a more dedicated focus became available with the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1983) and the Positive and Negative Syndrome Scale (PANSS: Kay, Fiszbein, & Opler, 1987). The SANS was important in drawing specific attention to negative symptoms in addition to the usual focus on positive symptoms or global ratings of psychopathology. It contains 25 items, takes approximately 30 min to administer, and includes five negative symptom domains: affective flattening/blunting, alogia, anhedonia-asociality, avolition-apathy, and attention. The fifth domain, attention, may be better conceptualized as a cognition variable.

The PANSS (Kay et al., 1987) was developed with similar structure to the BPRS (Overall & Gorham, 1962). The PANSS includes subscales for positive, negative, and general symptoms. It contains 30 items and takes 30–40 min to administer. The PANSS negative symptom subscale includes seven negative symptom items: blunted affect, lack of spontaneity and conversation flow, passive apathetic social withdrawal, active social avoidance, poor rapport, emotional withdrawal, and motor retardation. Some items are rated based on observation alone; however, two items are rated based on informant input as well as observation: emotional withdrawal and passive/apathetic social withdrawal.

The SANS and PANSS have received widespread use in clinical trials. These scales became the standard in the field; however, it has become clear that they have limitations in construct validity. For example, these scales include negative symptom items more closely tied to cognitive impairment or disorganization than negative symptoms (e.g., poverty of content of speech, inappropriate affect, attention) (Daniel, 2013). Furthermore, the SANS and the PANSS were incomplete in their assessment of negative symptoms and failed to separate negative symptoms from common extrapyramidal effects. The Negative Symptom Assessment (NSA: Alphs, Summerfelt, Lann, & Muller, 1989) was developed in part to account for this problem. Multiple versions of the NSA exist, including a 16-item version (Axelrod, Goldman, & Alphs, 1993) and a briefer 4-item version (Alphs et al., 2011). The negative symptom domains included by the NSA-16 are emotional/affective dysfunction, dysfunction in sociality, motivational dysfunction, and reduced psychomotor activity. The domains included in the 4-item version are restricted speech quality, emotion (reduced range), reduced social drive, and reduced interests. The NSA has played an important role in the measurement of negative symptoms in clinical trials, allowing rapid and reliable assessment of the negative symptom construct. However, similar to other scales, the NSA items also had issues with construct validity.

To address limitations with the aforementioned scales, as well as other problems related to the etiology and treatment of negative symptoms, the NIMH held a consensus development conference in 2005. At this meeting, several important

Table 3 Negative symptom domains identified in the 2005 NIMH consensus meeting (Kirkpatrick et al., 2006)

Domain	Description
Blunted affect	A decrease in the outward expression of emotion in the face, voice, or body gestures
Alogia	A reduction in the quantity of speech
Asociality	A reduction in social activity and decreased interest in close relationships
Anhedonia	A reduction in the intensity or frequency of pleasurable experience
Avolition	A reduction in the initiation of and persistence in activities

conclusions emerged. Among them were the five commonly accepted negative symptom constructs: blunted affect, alogia, asociality, anhedonia, and avolition (see Table 3 for descriptions of each and Kirkpatrick et al. (2006) for the conference consensus conclusions). As a result of this NIMH consensus meeting, two groups were formed that created two next-generation NSAs, the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011) and Clinical Assessment Interview for Negative Symptoms (CAINS: Kring et al., 2013).

Both the BNSS and the CAINS contain 13 items that assess the five negative symptom domains identified at the NIMH consensus meeting. Manuals, workbooks, score sheets, and gold standard training videos are available for both scales. Both measures are intended for use in clinical trials and experimental psychopathology studies. Administration time for the interview developed for each scale differs, with the BNSS taking approximately 10–15 min (average = 12 min) and 15–30 min (average = 22 min) for the CAINS. Table 4 summarizes scale characteristics and psychometric properties for the two scales. These next-generation measures represent important advances over older measures because they cover individual constructs according to current conceptualizations and eliminate items that have been found to relate more to other domains of pathology, such as disorganization and cognition (Blanchard, Kring, Horan, & Gur, 2011; Kirkpatrick et al., 2011).

The BNSS was designed with several principles in mind:

1. That it be concise and applicable for use in large, multicenter clinical trials
2. Coverage of the five domains identified in the NIMH Consensus Development Conference, with a separate subscale for each construct (anhedonia, avolition, asociality, blunted affect, alogia), as well as an additional item for "lack of normal distress" that has been important in separating primary from secondary negative symptoms (Kirkpatrick et al., 2001; Strauss et al., 2012)
3. Cross-cultural validity of items included in the scale
4. Suitability for use in clinical trials and epidemiological or experimental psychopathology studies
5. Items covering multiple aspects of anhedonia, consistent with modern conceptualizations of the symptom (Gard et al., 2007; Strauss & Gold, 2012)
6. Items that separate internal experience and overt behavior for avolition and asociality

Table 4 BNSS and CAINS comparison (adapted from Strauss & Gold, under review)

	BNSS	CAINS
Scale elements		
Number of items	13	13
Interview duration	10–15 min	15–30 min
Published translations	Spanish, German, Italian (in process: Portuguese, Korean, Turkish, Dutch, French, Mandarin, Polish)	Spanish, German, Mandarin, Czech, French, Cantonese, Korean, Polish, Greek, Swedish, and Lithuanian
Negative symptom domains		
Anhedonia	Three items, measuring:	Six items, requiring a frequency count of days in which pleasurable events were experienced, including:
	• Intensity of past pleasure	• Frequency of past pleasurable activities (three items)
	• Frequency of past pleasure	• Frequency of expected future pleasurable activities, including recreational activities, social activities, and work/school
	• Intensity of expected future pleasure	
	All items evaluate pleasure in multiple aspects, including recreational activities, social activities, work/school, and physical pleasure	
Avolition	Includes items rating internal experience and behavior separately. Items assess avolition in recreation, work/school, and self-care. Items also consider the total amount of time spent inactive	Internal experience and behavior are rated together. Includes items rating motivation for work/school and recreation. Self-care is not rated
Lack of normal distress	Item is designed to capture the reduction in frequency and duration of negative emotion in response to situations that otherwise would elicit negative emotion-postulated to be used to separate out deficit and nondeficit SZ	Not rated
Asociality	Includes items that rate internal experience and behavior separately	Internal experience and behavior are rated concurrently. Contains separate items for family and friends/romantic relationships
Blunted affect	Includes items that assess vocal expressivity (divided into speed, volume, and pitch), facial expressivity, and expressive body gestures	Includes items assessing vocal expressivity (pitch only), facial expressivity, and expressive body gestures
Alogia	Includes separate items rating the amount of unprompted elaboration and the total amount of speech	Rates total amount of speech only

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Table 4 (continued)

	BNSS	CAINS
Psychometric analysis		
Inter-rater reliability	ICC—0.97 average total score	ICC—0.97 average total score
Internal consistency	Cronbach's alpha 0.93–0.94	Cronbach's alpha 0.93
Test-retest reliability	$r=0.93$ total, 0.92 for AA, 0.88 for DE	$r=0.69$ for MAP and 0.69 for DE
Discriminant validity	Low to null correlations between BNSS and PANSS/BPRS disorganized, positive, and depression scores	MAP and DE low to null correlations between CAINS and BPRS positive, agitation, extrapyramidal, depression
Convergent validity	Medium to high correlations between BNSS total and SANS, BPRS, and PANSS as well as functional outcome (community based). Moderate correlations with cognition	DE and MAP scales have moderate correlations with SANS total, BPRS and PANSS negative, functional outcome (community based). MAP correlated moderately with TEPS consummatory and anticipatory scales as well as Chapman social anhedonia. DE correlated with experimenter-coded facial expressions. Nonsignificant correlations with cognition and functional capacity
Factor structure	Two factors: MAP (anhedonia/asociality/avolition) and DE-(alogia/restricted affect)	Two factors: MAP (anhedonia/avolition/asociality) and DE (alogia, restricted affect)

7. Not including items that have been found to be more related to disorganization than negative symptoms, such as poverty of content of speech, inappropriate affect, and attention

All BNSS items are rated on a 7-point scale (ranging from 0 absent to 6 severe). A total score is developed by summing all items, and subscale scores are derived by averaging items in each of the six subscales. BNSS items evaluate content according to the most recent conceptualizations of individual negative symptoms. For example, in accordance with current neurobehavioral models of reward (Berridge & Robinson, 2003), the BNSS has an anhedonia item designed to assess anticipatory pleasure. Deficits in anticipatory pleasure have been demonstrated in prior studies, indicating that schizophrenia patients prospectively estimate less pleasure in the future compared to controls, whereas the ability to experience pleasure in the moment while engaged in the activity appears intact (Gard et al., 2007). Such deficits may contribute to why schizophrenia patients also engage in fewer instances of pleasurable activity during everyday life. Additionally, the BNSS avolition and aso-

ciality scales have separate items for internal experience and overt behavior, as there can be dissociations between these items that predict meaningful clinical processes (e.g., reduced social behavior may be based on reduced anticipation of pleasure or on paranoid guardedness). These items may be important for identifying treatment effects. For example, it may often be necessary to get patients behaviorally activated and have opportunities to counter maladaptive beliefs related to volitional activities and socializing before it is possible to shift internal experience (i.e., wanting to engage in activities).

Psychometric properties of the BNSS are excellent. Reliability has been demonstrated via test-retest scores, inter-rater agreement, and internal consistency (Kirkpatrick et al., 2011; Strauss et al., 2012). Convergent validity was also established by demonstrating high correlations with other negative symptom scales (e.g., SANS, PANSS, BPRS), measures of functional outcome, and neuropsychological impairment (Strauss et al., 2012). Discriminant validity has also been supported by low or nonsignificant correlations with measures of psychosis, disorganization, depression, and general symptoms (Kirkpatrick et al., 2011; Strauss et al., 2012).

Several recent studies also indicate that the BNSS has achieved one of its intended purposes related to cross-cultural utility. The BNSS has been or is in the process of being translated into several languages. Published translations of the BNSS now exist in Italian, Spanish, and German (Bischof et al., under review; Mané et al., 2014; Merlotti, Mucci, Bucci, Nardi, & Galderisi, 2014). Psychometric properties of the translated scales have been good and comparable to the original English version (Bischof et al., under review; Mané et al., 2014; Mucci et al., 2015).

The Collaboration to Advance the Negative Symptom Assessment of Schizophrenia (CANSAS: Blanchard et al., 2011) was established to develop the CAINS, using a transparent, iterative, and data-driven process that took multiple years to complete. It was designed to integrate three principles: the environmental context, individual behavior, and self-report of internal states (Carpenter, Blanchard, & Kirkpatrick, 2016). The original, i.e., beta, version of the CAINS contained 23 items (Forbes et al., 2010; Horan, Kring, Gur, Reise, & Blanchard, 2011). An oversampling of items from the five consensus domains was initially conducted to allow for a rigorous data-driven approach that whittled the items down to those that were most psychometrically sound and valid. Items were found to load on two dimensions in factor analysis, one reflecting motivation and pleasure (MAP) and the other diminished expressivity (EXP). Classical test theory and item response theory were used to delete, retain, and modify item content, anchors, and probes. Several items found to be highly correlated with other items were considered redundant, and other items that did not load cleanly onto factor dimensions were eliminated to bring the final version of the scale to 13 items (Horan et al., 2011).

Kring et al. (2013) validated the final scale in a sample of 162 schizophrenia patients. Factor analysis confirmed the same two-factor structure identified in the beta version. Inter-rater agreement of the final 13-item scale was good across the four sites, including both of the subscales. Test-retest reliability was adequate, and estimates of internal consistency indicated that items in the subscales adequately reflected single constructs. Convergent validity was demonstrated via moderate

associations with the SANS and BPRS negative symptom subscale and a measure of functional outcome. CAINS anhedonia items were also significantly correlated with questionnaires assessing anticipatory pleasure and social anhedonia. Discriminant validity was demonstrated via low correlations with psychosis, agitation, and extrapyramidal symptoms. The CAINS has recently been evaluated across 15 different sites; factor structure was confirmed (Blanchard et al., under review). The CAINS is in the process of being translated into several languages. Published cross-cultural validation studies have been completed in German, Spanish, and Mandarin (Chan et al., 2015; Engel, Fritzsche, & Lincoln, 2014; Valiente-Gómez et al., 2015). Translations also exist in Czech, French, Cantonese, Korean, Polish, Greek, Swedish, and Lithuanian (Carpenter, Blanchard, & Kirkpatrick, 2016). These validation studies indicate that the translations have psychometric properties comparable to the English version.

CAINS MAP items have several important advantages (Blanchard et al., 2011; Horan et al., 2011). Anhedonia items evaluate the frequency of pleasure experienced over the past week and frequency of expected future pleasure over the next week. Questions cover domains of work/school, recreational activities, and social interactions. The CAINS anticipatory pleasure items evaluate the number of enjoyable activities that patients expect to experience throughout the next week in relation to work, social, and recreational domains. The items are designed to assess a patient's ability to spontaneously generate predictions of how many pleasurable activities they will experience, a form of anticipatory pleasure deficit. The CAINS anhedonia items therefore focus on frequency of expected and remembered pleasure, in line with modern theories of anhedonia and reward (Gard et al., 2007). The avolition and asociality items also consider the inner experience and overt behavior aspects of pathology, thereby capturing a more apathetic form of pathology that is thought to be core to the negative symptom construct rather than a secondary factor.

There may still be some lingering construct validity issues with the five negative symptom domains identified at the MATRICS consensus meeting that may not be addressed by the BNSS or CAINS. For example, there is considerable debate as to how anhedonia should be conceptualized. Laboratory and experience sampling studies indicate that people with schizophrenia do not evidence a reduction in self-reported positive emotion or arousal to pleasant stimuli (Cohen & Minor, 2010; Gard et al., 2007; Llerena, Strauss, & Cohen, 2012; Oorschot et al., 2013). Such evidence contradicts observations from clinical rating scales, such as the BNSS, CAINS, or SANS, which indicate that hedonic experience is diminished in most persons with schizophrenia. Trait emotional experience questionnaires, such as the Positive and Negative Affect Scale and the Chapman Anhedonia Scales, also indicate that people with schizophrenia report less pleasure than controls (Horan, Kring, & Blanchard, 2006). Several accounts have been proposed to explain this discrepancy (Cohen et al., 2011; Barch & Dowd, 2010; Gold et al., 2008; Kring & Moran, 2008; Strauss & Gold, 2012). For example, it may be that anhedonia does not reflect a deficit in consummatory, or in-the-moment, pleasure, but rather a deficit in anticipating pleasure from future activities (Gard et al., 2007; Kring & Barch, 2014; Kring & Elis, 2013). Or, discrepancies may reflect certain psychological processes

that are commonly used to complete emotional self-reports that use retrospective and trait formats, such as semantic emotion knowledge, or beliefs about how one generally feels which may be inaccurate and subject to reporting biases (Strauss & Gold, 2012). Anhedonia may reflect an emotional memory deficit that impacts retrospective reports of pleasure such as those obtained in clinical interviews where clinicians ask patients to report their intensity or frequency of pleasurable events over timeframes as long as the past week, past 2 weeks, or even past month (Strauss & Gold, 2012). Alternatively, anhedonia may reflect a behavioral deficit characterized by reduction in pleasure seeking activity, which stems from a dissociation between intact "liking" and impaired "wanting" (Heerey & Gold, 2007). Similarly, avolition may have multiple components, including a subjective component of inner experience (i.e., how much someone wants to engage in behavior) and an objective component reflecting how much someone actually engages in behavior. Furthermore, neither scale accounts for the primary-secondary negative symptom distinction problem that has affected all rating scales other than the SDS. On both the BNSS and CAINS, two individuals can receive the exact same ratings for very different reasons (e.g., reduced volitional behavior due to apathy vs. paranoia). The scales have tried to account for this somewhat by gearing item descriptions and anchors toward rating more primary than secondary constructs; however, secondary factors will invariably be weighted and contribute to scores assigned. Future developments might consider specifying the source of negative symptoms, as done on the SDS. Thus, several issues remain to be resolved with regard to modern conceptualizations of negative symptoms, and further research is needed to refine these constructs and improve the validity of current rating scales. Nonetheless, for application in clinical assessment, the CAINS and BNSS represent the most up-to-date representation of the negative symptom construct.

Information on accessing these two scales and training materials is available together with a brief description of each measure (Carpenter, Blanchard, & Kirkpatrick, 2016).

Negative Symptoms Are a Multidimensional Construct

Early factor analytic studies indicating that negative symptoms were a domain of pathology distinct from other forms of pathology were generally regarded as evidence that negative symptoms represent a single domain of pathology. However, more recent research suggests that this is not the case, indicating the negative symptoms may actually be multidimensional. For example, both the BNSS and CAINS produce a two-factor solution (Horan et al., 2011; Kring et al., 2013; Strauss et al., 2012). The two negative symptom dimensions that have been consistently identified reflect (1) diminished MAP, including anhedonia, avolition, and asociality items, and (2) diminished expressivity (EXP), which consists of alogia and blunted affect items. A similar factor structure has been found in some studies of the SANS and the SDS (for a review, see Blanchard & Cohen, 2006).

These two factors may have distinct underlying etiology. For example, the MAP dimension has been associated with aberrant cortico-striatal connectivity that is associated with impairment in several aspects of reward processing, including reinforcement learning, effort-cost computation, value representation, reward anticipation, uncertainty-driven exploration, and action selection (Barch & Dowd, 2010; Gold et al., 2008; Strauss et al., 2014). In contrast, the diminished expressivity dimension has most strongly been tied to cognitive impairments. For example, experimentally increasing cognitive demand causes alogia and blunted affect symptoms to become more severe (Cohen, Najolia, Kim, & Dinzeo, 2012).

These dimensions, however, may not be uniformly impactful on clinical outcomes. For example, there is some evidence that the MAP dimension may be associated with poorer outcomes than the expressivity dimension, including general and social cognition, functional outcome, subjective well-being, and recovery (Strauss, Harrow, Grossman, & Rosen, 2010; Strauss et al., 2012, 2013; Fervaha, Foussias, Agid, & Remington, 2013; Foussias & Remington, 2010).

Strauss et al. (2013) also demonstrated that not only can items on negative symptom scales load onto these two distinct dimensions, but patients themselves can be reliably subgrouped according to negative symptom profiles determined by their relative balance of MAP and EXP symptoms. They used cluster analysis to identify two groups of patients, one with more severe MAP and lower EXP and the other with high EXP and low MAP. Discriminant function analysis confirmed the validity of these two subgroups, indicating that they were adequately separated and that few group misassignments occurred based on the clustering procedures. Most importantly, the two subgroups differed on a number of external validators, such as psychotic symptoms, social cognition, duration of hospitalization, and functional outcome. The group characterized by severe MAP and less impaired EXP had overall poorer outcome than the group with severe EXP and lower MAP. This may suggest that MAP is a more severe dimension of negative symptom pathology. It is also possible that MAP and EXP are separate pathways for therapeutic discovery.

Dimensional vs. Categorical Structure of Negative Symptoms

The aforementioned cluster analysis study also raises an important question—what is the structure of negative symptoms? Factor analytic studies have generally been taken as evidence that negative symptoms are dimensional in nature, i.e., patients vary in degree of severity from absent to severe. However, evidence from studies on the deficit syndrome (Kirkpatrick et al., 2001) provide some indication that negative symptoms may be better conceptualized in terms of a categorical framework, i.e., patients vary in kind, with symptoms that are either present or absent. The issue of structure is an important one, as it has implications for how the etiology of negative symptoms should be studied. For example, if categorical, efforts to subgroup patients would be beneficial because etiological factors should vary as a function of the presence or absence of pathology. If dimensional, regression-based methods

such as those proposed for use in the NIMH RDoC initiative would be most appropriate in identifying etiological factors that vary along a continuum of health to illness. Alternatively, negative symptoms may reflect a hybrid categorical-dimensional structure, where once past a certain threshold of severity, patients can be seen as unique in kind, with the magnitude of severity above this level being important for predicting outcome. At present, it is unclear whether negative symptoms are dimensional, categorical, or hybrid in structure—there has been evidence for each. For research and clinical application, a severity dimension can be defined regardless of structure.

Multivariate statistical approaches, such as taxometric analysis and latent mixture modeling, are starting to provide some insight into these questions. Blanchard, Horan, and Collins (2005) used taxometric analysis to evaluate negative symptom structure in a sample of 238 schizophrenia patients. They found a distinct taxonomic latent structure with a base rate of 28–36 %, indicating a distinct class of individuals with higher negative symptoms. This sample of patients was also externally validated, as this group of patients was mostly male and demonstrated poorer social functioning than the rest of the patient sample, while remaining comparable in symptoms not related to the taxon. A second study by Ahmed, Strauss, Buchanan, Kirkpatrick, and Carpenter (2015) used taxometric analysis and latent mixture modeling to replicate and extend the results of Blanchard et al. (2005) in a sample of 789 patients. Results supported the existence of a nonarbitrary boundary that distinguished patients at being part of a negative symptom taxon. The negative symptom taxon was distinguished by primary and enduring negative symptoms and had high overlap with the clinically diagnosed deficit schizophrenia subtype. These findings at first glance supported the categorical structure of negative symptoms; however, mixture modeling and taxometric analysis also provided some evidence consistent with a hybrid structure, where negative symptoms maintained categorical and dimensional elements that identified aspects of phenomenology. For example, within the negative symptom subtype, dimensionality was an important predictor of several outcome variables. Thus, the long-standing debate of dimensional vs. categorical structure may be one that can be adequately resolved by considering a hybrid alternative. Indeed, schizophrenia patients may have a negative symptom pathology or not, but when the pathology is present, it is the degree of pathology that may determine their outcome rather than simply being a member of the class. This hybrid structure has important implications for assessment and treatment. For example, this finding may help to explain previous ambiguous findings in research. It may also point to the existence of a negative symptom class in other disorders, opening the door for studies utilizing the dimensional NIMH Research Domain Criteria (RDoC) framework. Finally, the taxonomic structure may inform phenotypes used in genetic and environmental studies aimed at establishing causal pathways.

Negative symptoms may not be the only domain of schizophrenia pathology where the structure of symptom presentation has important implications. The heuristic value of domains of pathology is substantial. Many psychopathologies associated with the schizophrenia concept can be identified and segregated for specific investigation. Eight domains are defined as dimensions in Section 3 of DSM-5 as

relevant across the psychosis chapter as the essential clinical targets for assessment and treatment of individual patients. Other domains are relevant ranging from impaired insight to neurologic soft signs. The psychopathology domains can map onto behavioral phenotypes to advance animal models relevant to aspects of schizophrenia. They provide the clinical targets that need to be informed by the RDoC initiative with fundamental knowledge of neural circuits and behavioral constructs to advance knowledge, treatment, and prevention of mental illnesses related to psychotic disorders. The domains approach has already altered the structure of therapeutic development. The recognition that antipsychotic drugs initiating effects at the dopamine D2 receptor do not have efficacy for primary negative symptoms or cognition impairments has defined the major unmet therapeutic needs in schizophrenia. The FDA has joined a consensus on clinical trial designs necessary to avoid pseudo-specific effects on rating scale assessments and gain an indication for negative symptoms (April 2006) or cognition (Jan, 2005). The neural circuit dysfunction and behavioral constructs relevant for specific domains can be hypothesized and tested. For example, a current RDoC project is based on MRI findings related to primary negative symptoms and hypothesized to be relevant to social cognition. This hypothesis can be tested within schizophrenia where negative symptom variability is large and on a continuum between severe deficit schizophrenia and non-ill volunteers.

Summary and Conclusions

The concepts and investigations reviewed above suggest the following:

- Schizophrenia is a clinical syndrome that can be deconstructed into meaningful domains of psychopathology.
- Individual patients vary substantially on which domains are present as well as severity.
- Negative symptoms are common in persons with schizophrenia, but only primary negative symptoms are a manifestation of schizophrenia psychopathology in the "weakening of the wellsprings of volition" sense that Kraepelin described.
- The failure to distinguish primary from secondary negative symptoms has profound consequences as viewed in the vast majority of clinical trials that report negative symptom efficacy without regard for causation and without controlling for pseudospecificity.
- Schizophrenia is now broadly defined with positive psychotic symptoms, and a subgroup with primary negative symptoms is a candidate disease entity.
- Evidence of negative symptoms as a taxon supports the separate classification of persons with primary negative symptoms.
- Negative symptoms are an unmet therapeutic need.
- Two factors best define the negative symptom construct and these may have different pathophysiological and treatment implications.

- The avolitional component may not be based on a diminished capacity to experience pleasure, but difficulty using mental representations of affective value to guide decision-making and goal-directed behavior.

Part II in this volume by Strauss et al. will address the range of laboratory-based investigations of negative symptoms, clarify current hypotheses and theories concerning negative symptom pathology, and address future directions for negative symptom research and clinical care.

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