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A REVIEW OF NEGATIVE SYMPTOM ASSESSMENT STRATEGIES IN YOUTH AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Abstract

Studies attempting to deconstruct the heterogeneity of schizophrenia and the attenuated psychosis syndrome consistently find that negative symptoms are a core dimension that is distinct from other aspects of the illness (e.g., positive and disorganized symptoms). Negative symptoms are also highly predictive of poor community-based functional outcomes, suggesting they are a critical treatment target. Unfortunately, pharmacological and psychosocial treatments for negative symptoms have demonstrated limited effectiveness. To address this critical unmet therapeutic need, the NIMH sponsored a consensus development conference to delineate research priorities for the field and stimulate treatment development. A primary conclusion of this meeting was that next-generation negative symptom rating scales should be developed to address methodological and conceptual limitations of existing instruments. Although second-generation rating scales were developed for adults with schizophrenia, progress in this area has lagged behind for youth at clinical-high risk (CHR) for developing psychosis (i.e. those meeting criteria for a prodromal syndrome). Given that negative symptoms are highly predictive of the transition to diagnosable psychotic illness, enhancing our ability to detect negative symptoms in CHR youth is paramount.

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Contributors

The idea for the manuscript was developed by Drs. Strauss and Mittal, who wrote the first draft of the paper. All other authors contributed to subsequent drafts.

Conflicts of Interest

G.P.S. is one of the original developers of the Brief Negative Symptom Scale (BNSS) and receives royalties and consultation fees from Medavante-ProPhase LLC in connection with commercial use of the BNSS and other professional activities; these fees are donated to the Brain and Behavior Research Foundation. GPS has received honoraria and travel support from Medavante-ProPhase LLC for training pharmaceutical company raters on the BNSS. In the past 2 years, GPS has consulted for and/or been on the speaker bureau for Minerva Neurosciences, Acadia, and Lundbeck pharmaceutical companies. VAM, APB, KFV, and EFW have no relevant disclosures to report.

The current paper discusses conceptual and methodological limitations inherent to existing scales that assess negative symptoms in CHR youth. The theoretical and clinical implications of these limitations are evaluated. It is concluded that new scales specifically designed to assess negative symptoms in CHR youth are needed to accurately chart mental illness trajectories and determine when, where, and how to intervene. Recent efforts to develop next-generation measures designed specifically for CHR youth to meet this urgent need in the field are discussed. These new approaches offer significant progress for addressing issues inherent to earlier scales.

Keywords

Prodrome; anhedonia; avolition; asociality; alogia; blunted affect

Overview

Negative symptoms, defined as reductions in motivation, emotion, and/or expressive behavior (Strauss and Cohen, 2017), are a core feature of schizophrenia (Bleuler, 1950; Kraepelin, 1919) and the attenuated psychosis syndrome (Piskulic et al., 2012). Studies confirm that negative symptoms are distinct from other dimensions of the illness (e.g., positive and disorganized symptoms) (Buchanan and Gold, 1996; Peralta et al., 1992; Strauss et al., 1974), and that they predict a number of poor clinical outcomes that limit social and vocational attainment (Fervaha, 2014; Foussias et al., 2014). Unfortunately, attempts to remediate negative symptoms using pharmacological and psychosocial interventions have been ineffective, and no medication has received an indication for negative symptoms by the FDA (Fusar-Poli et al., 2015).

To address this critical unmet need in schizophrenia-spectrum therapeutics, the NIMH sponsored a consensus development conference in 2005 to delineate priorities for research and promote the development of innovative treatment approaches. Several key conclusions resulted from this meeting (Kirkpatrick et al., 2006). Paramount among these were that there are at least 5 core domains of negative symptoms (anhedonia, avolition, asociality, alogia, blunted affect) and new negative symptom rating scales are needed to assess these domains according to current conceptualizations (Kirkpatrick et al., 2006). Two next-generation negative symptom rating scales resulted from the 2005 NIMH consensus conference: the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013) and the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011). The CAINS and BNSS were designed to assess negative symptoms according to current conceptualizations of the 5 consensus domains. Evaluations of the psychometric properties of the BNSS and CAINS indicate good inter-rater agreement, test-retest reliability, internal consistency, and convergent/discriminant validity (Horan et al., 2011; Kring et al., 2013; Strauss and Gold, 2016; Strauss et al., 2012a; Strauss et al., 2012b). Initial exploratory factor analytic studies examining the structure of the scales suggested that the five negative symptom domains load onto two dimensions: motivation/pleasure (MAP) (anhedonia, avolition, asociality) and diminished expressivity (EXP) (blunted affect and alogia). However, subsequent studies using confirmatory factor analysis and network analysis have supported a five-factor model with individual factors corresponding to the 5 consensus domains (Ahmed et al., 2019;

Strauss et al., 2018, 2019ab). The BNSS and CAINS have become widely used in experimental psychopathology and clinical trials in schizophrenia (Carpenter et al., 2015; Strauss and Gold, 2016).

Despite this progress, the NIMH consensus conference did not discuss the development of negative symptom scales specific to youth at clinical-high-risk (CHR) for developing psychosis (i.e. adolescents/young adults meeting criteria for a prodromal syndrome). The onset of psychosis is usually preceded by a prodromal phase characterized by functional decline and subtle attenuated symptoms that progressively worsen over the course of several years (Cannon et al., 2008b; Haroun et al., 2006). This period is of interest both as a window for investigating processes involved in illness onset, and as a potential point of intervention and prevention (Haroun et al., 2006; McGlashan et al., 2007; Mittal et al., 2010). Although improvements in early identification methods may have led to a decrease in rates of transition among CHR youth (Yung and McGorry, 1997), a substantial proportion of those at risk (anywhere from 10–35%) will still develop a psychotic disorder within two years following initial assessment (Cannon et al., 2008a; Yung et al., 2007) and many manifest serious mood disorders at follow-up that require treatment (Addington et al., 2017).

Improved assessment of negative symptoms may be crucial for enhancing early identification and prevention efforts for several reasons. First, negative symptoms typically appear years before the onset of attenuated positive symptoms and are one of the earliest indicators of risk (Zhang et al., 2020). Unlike positive symptoms, they are more likely to be persistent, rather than episodic (Piskulic et al., 2012; Carrion et al., 2016). They are often the reason why individuals make initial contact with the treatment system (Yung & McGorry, 1996). Accurately assessing negative symptoms early in the prodromal period when youth first enter the treatment system may allow clinicians to initiate efforts aimed at preventing the cascade that leads to psychosis. Second, negative symptoms are highly prevalent in the prodromal phase (Lencz et al., 2004; Corcoran et al., 2011; Carrion et al., 2016; Azar et al., 2018). For example, in a North American Prodromal Longitudinal Study (NAPLS) study, 82% of CHR cases were rated as having one or more negative symptoms at moderate severity (Piskulic et al., 2012). Despite this high prevalence and evidence that negative symptoms are a strong predictor of the probability of transitioning to a formal psychotic disorder (Piskulic et al., 2012; Alderman et al., 2015; Zhang et al., 2020; Healey et al., 2018; Brucato et al., 2017; Demjaha et al., 2012; Valmaggia et al., 2013; Velthorst et al., 2009; Werbeloff et al., 2015), existing clinical instruments do not take negative symptoms into account when making the prodromal syndrome classification. This approach is inconsistent with literature speaking to the importance and prognostic value of negative symptoms, as well as how schizophrenia is diagnosed in the DSM-5, which includes negative symptoms as a core feature of criterion A (American Psychiatric Association, 2013). Third, negative symptoms are highly associated with community-based functional outcomes in CHR youth (Carrion et al., 2018; Minichino et al. 2017; Schlosser et al. 2012). Failure to assess negative symptoms early in the prodromal phase may therefore miss an important opportunity for better understanding their course, prognostic significance, interventions aimed at preventing decline in social and occupational functioning. Once schizophrenia onsets, it often limits the most productive years of an individual's life (Wu et al., 2005) and produces enormous public health costs, as a leading medical cause of functional disability in the United States

(Salomon et al., 2012). Given the aforementioned evidence, enhancing the detection of negative symptoms in CHR youth is paramount because it will improve our ability to accurately chart mental illness trajectories and determine when, where, and how to intervene more effectively to prevent this serious and debilitating illness.

Now that the CHR research paradigm has become established in the field, it is important that its focus be broadened. Because positive symptoms have remained the defining symptoms of psychosis in the DSM, it is understandable that their presence, in an attenuated form, would be the initial emphasis of CHR instruments. Although scales currently in widespread use have provided invaluable information regarding the frequency/severity, course, and prognostic significance of negative symptoms in those at CHR (Piskulic et al., 2012; Carrion et al., 2016; Zhang et al., 2020), these measures have certain conceptual and methodological limitations. Addressing these limitations is critical for producing rapid advancements in identifying treatment targets and translating these into interventions. In the current manuscript, we discuss the limitations associated with CHR measures of negative symptoms, as well as recent progress in overcoming these issues via next-generation negative symptom assessment approaches.

Issues with Existing Scales

In North America, the Structured Interview for Prodromal Syndromes (SIPS: Miller et al., 2003) is the most widely used instrument for assessing symptom severity and making attenuated psychosis syndrome (APS) classifications. Although the SIPS is well-validated, widely used, and has been vital to progress in the identification and prevention of psychosis, there are several conceptual and methodological limitations associated with its negative symptom subscale. Similar issues impact scales more commonly used outside of North America, including the Comprehensive Assessment of At Risk Mental States (CAARMS: Yung et al., 2002) and Schizophrenia Proneness Instrument (SPI: Diaconescu et al., 2011; Schultze-Lutter et al., 2012).

Conceptual Issues

There are several conceptual issues common to the negative symptom items on the SIPS, CAARMS, and SPI (see Table 1):

(1) Inclusion of items based on outdated conceptualizations of negative symptoms.—None of the aforementioned scales cover all 5 domains agreed upon in the NIMH consensus conference (Kirkpatrick et al., 2006) and the negative symptom scale items are nonspecific and conflate constructs. Such issues make it difficult to determine which psychological processes are reflected in ratings of individual items and weaken the ability to observe treatment effects.

The SIPS negative symptom items include: social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, and occupational functioning. Each of these items has construct validity issues. The *social anhedonia* item conflates asociality, social anxiety, and social skill; although termed social anhedonia, it does not evaluate pleasure specifically. It also fails to evaluate pleasure across a comprehensive range

of relevant contexts (e.g., physical, recreational, role). The *expression of emotion* item conflates blunted affect and alogia via anchors that focus on difficulty "sustaining conversation," ultimately failing to separate out channels of communication (facial, vocal, body). The *experience of emotion and self* item does not distinguish between the experience of positive and negative emotions, requiring raters to make judgments about emotion as a singular construct independent of valence. The *ideational richness* item is not part of the negative symptom construct, and the *occupational functioning* item is more conceptually related to measures of functional outcome than negative symptoms.

Similarly, the CAARMS obscures some potentially important distinctions among negative symptom dimensions. It includes three items under its negative symptom section: alogia, avolition/apathy, and anhedonia. Items relevant to asociality (social isolation), avolition (impaired role function), anhedonia (subjective emotional disturbance), and blunted affect (observed blunted affect) are also included in the emotional disturbance and behavioral change subscales. These items each have certain conceptual limitations. The alogia item incorporates both participant self-report and observed speech behavior. Self-report is typically not evaluated when rating alogia due to poor insight into this symptom. The alogia item is also conflated with disorganization, as it evaluates constructs like thought blocking and "vagueness". The avolition/apathy item does not incorporate persistence, only initiation. The source of initiation is not considered, although determining the impetus for behavior is critical for assessing the construct. The anhedonia item assesses interest, which although part of the conceptualization of this symptom in depression, is typically not included in schizophrenia-spectrum disorders per modern conceptualization. The subjective emotional experience item includes elements of inappropriate affect, which is more conceptually relevant to disorganization. This item also evaluates reductions in both positive and negative emotions in one item, even though they may show dissociations (Kirkpatrick et al., 2011). The observed blunted affect item factors in rater rapport, rather than a judgment purely based on behavioral observation. The social isolation item includes "feeling uncomfortable" around others as a rating criterion, which is more related to social anxiety.

Unlike the SIPS and CAARMS, the SPI-A and SPI-CY does not have a specific negative symptom subscale. However, the SPI-CY does include items that map on to negative symptom domains. For example, the measure assesses for reduced energy and vitality, reduced persistence and patience, reduced drive and initiative, decrease in positive emotional responsiveness towards others, decreased need for social contacts, and disturbances of expressive speech. Although these items do overlap with current negative symptom conceptualizations, their scope remains limited and they contain multiple conceptual issues. In particular, these items focus on inner-experience measured via self-report and fail to evaluate overt behaviors that are critical for assessing negative symptoms. Table 1 summarizes the conceptual limitations affecting these measures.

(2) Failure to separate out experiential and objective components of avolition and asociality.—There are often dissociations between objective and experiential processes, which have important implications for treatment. For example, an individual may withdraw socially due to anxiety or paranoia (and thus have an objective deficit in terms of frequency of social activity), but care about social interactions and focus on them a great

deal (and thus have no deficit experientially). The SIPS, SPI, and CAARMS fail to evaluate behavior and inner-experience separately. Having separate items is important for measuring treatment change, as these items may show improvement at different rates or sequences (Strauss et al., 2012a; Strauss et al., 2020).

(3) Failure to incorporate relevant contemporary research findings from the basic affective science literature to measure anhedonia.—Basic science now distinguishes between consummatory and anticipatory components of pleasure, which are key to modern conceptualizations of anhedonia in schizophrenia (Frost and Strauss, 2016). Next-generation negative symptom assessments developed for adults with schizophrenia emphasize separating out different components of pleasure in the assessment of anhedonia (Kirkpatrick et al., 2011; Kring et al., 2013); however, this differentiation is lacking in the SIPS, CAARMS, and SPI.

(4) Failure to isolate "primary" negative symptoms or take the role of "secondary" negative symptoms into account.—*It is now well established that n*egative symptoms can be primary (i.e., idiopathic) manifestations of the disease process itself or secondary to other features, such as depression, anxiety, psychosis, disorganization, and antipsychotic medications (Kirkpatrick et al., 2001). Current CHR/APS scales do not account for sources of secondary negative symptoms, despite the high prevalence of comorbid depression and anxiety in this population (Addington et al., 2011). This is problematic because two individuals could receive the exact same scores on a negative symptom item for two very different reasons. It is therefore unclear whether ratings reflect "true" negative symptoms or other factors that sometimes mask as negative symptoms. From a clinical perspective, this is problematic because scores on existing scales do not inform treatment/prevention. From a research perspective, failure to account for secondary causes makes it difficult to isolate pathophysiological mechanisms tied to individual symptoms, which do not reflect homogeneous processes as rated by current scales.

(5) Limited coverage of the range of motivational and social problems that occur during adolescence/early adulthood.—Subsequent to the development of most CHR diagnostic instruments, social and motivational behavior has changed considerably due to rapid advances in mobile technology and the Internet. Social interactions via text messages and social media are becoming increasingly the norm among today's youth, with the past decade seeing a 152% increase in time spent online among Americans (Group, 2001–2015). High internet use is almost universal in adolescents and young adults, with roughly 17 hours per week spent online, much of which is spent on social media and electronic social interactions (Derbyshire et al., 2013; Interactive, 2003). CHR youth spend an even greater amount of time online than healthy controls, especially with regard to social media, chat room use, and other electronic social communications, despite having fewer social interactions in-person (Mittal et al., 2007; Pelletier-Baldelli et al., 2015). Electronic and social media use is not adequately assessed by existing scales. The aforementioned measures place value on in-person interactions only, failing to explicitly take into account how youth commonly interact today- over electronic media. This type of social behavior has become incredibly prevalent, and it is too important to discount.

(6) Failure to reduce the influence of cognitive impairments.—Cognitive impairment is common to both schizophrenia and CHR populations (Dickinson et al., 2007; Brewer et al., 2006). Prior studies demonstrate a medium association between negative symptoms and cognitive impairment in schizophrenia and CHR (Harvey et al., 2006; Leanza et al., 2018; Chu et al., 2019). It is unclear to what extent this reflects methodological artifact or genuine construct overlap. For example, the SIPS and CAARMS each assess negative symptoms using retrospective interviews with a lengthy timeframe. Retrospective interviews, particularly those using wider reporting intervals, are known to reduce the validity of clinical negative symptom ratings that are impacted by long-term and working memory impairments (Strauss & Gold, 2012). Newer negative symptom scales designed for schizophrenia (Kirkpatrick et al., 2011; Kring et al., 2013) have adopted shorter, one-week timeframes to account for this issue. Such procedures are not yet standard in CHR negative symptom interviews.

Methodological Issues:

The SIPS, CAARMS, and SPI-A/SPI-CY items also have several methodological limitations that are common to each scale (see Table 2):

(1) Limitations Associated with Scale Development: Each of the aforementioned scales also has certain psychometric limitations that stem from their development and validation processes. Modern negative symptom rating scales designed for adults with schizophrenia (i.e., CAINS, BNSS) were developed based on an expert consensus meeting, polling across the field, and multiple iterative psychometric validation studies conducted on large and representative samples (Strauss et al., 2012a; Kring et al., 2013). Such procedures were not systematically undertaken for CHR scales, which were developed in an earlier era when such processes were atypical in psychiatry. Much like the scales developed for schizophrenia during this era, such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the SIPS, CAARMS, and SPI were derived using clinical fiat and conceptual formulations of their time. Individual research groups developed the scales without broader consensus from the field regarding which negative symptom constructs should be included or how they should be defined. Initial scale validation was based on small samples that were not diverse or broadly representative of the CHR population (Miller et al., 2002; Yung et al., 2005; Schultze-Lutter et al., 2014; Schultze-Lutter et al., 2004; Gross et al., 1987; Olsen and Rosenbaum, 2006). These issues resulted in negatve symptom subscales that were not developed, validated, or refined based on empirical considerations.

(2) Psychometric Limitations: Failure to derive scales based on an iterative, data-driven process has also resulted in suboptimal psychometric properties for negative symptom items within the SIPS, CAARMS, and SPI. For example, the structure of negative symptom items within the CAARMS and SPI is unclear. The SPI does not formally have a negative symptom subscale, and the CAARMS has items within other subscales that are putatively part of the negative symptom construct. Without exploratory and confirmatory factor analytic studies, it is unclear whether the items conceptualized as being part of the negative symptom construct validly fall within that dimension or whether items from other constructs

should fall within this dimension. A recent exploratory factor analysis was conducted on the negative symptom items of the SIPS, indicating the presence of two dimensions reflecting diminished motivation and emotional expression (Azis et al., 2019). Although these two dimensions have also been found using exploratory factor analyses of the BNSS, CAINS, and SANS (Horan et al., 2011; Kring et al., 2013; Strauss et al., 2012; Blanchard & Cohen, 2006), problems with construct validity of the SIPS negative subscale prevent these factors from mapping onto the motivation/pleasure and emotional expression factors typically found in schizophrenia. Azis et al. (2019) also found that not all SIPS negative subscale items loaded onto the two dimensions, further suggesting that item removal may be warranted. Furthermore, the SIPS, CAARMS, and SPI use single items to assess entire domains of negative symptoms, even though single item scales are known to have poor psychometric properties (Gliem & Gliem, 2003). This procedure is suboptimal for deriving domain specific subscales, as has been done on the BNSS and CAINS. Finally, unlike the anchor scaling for positive symptom items, scaling for negative symptom items on these scales is imprecise. The anchors are not designed to cover the full range of attenuated to severe negative symptom pathology. As result, these items tend to be positively skewed and do not allow for assessment of fine-grained changes in negative symptom severity. Extensive psychometric validation of the negative symptom subscales on the SIPS, CAARMS, and SPI should be undertaken to determine whether item refinement or deletion is needed based on item response theory and classical test theory analyses.

(3) Limited Training Materials: Not all scales have developed standardized materials for training and those that have been developed are problematic. For example, no training materials or videos exist for the SPI; its manual must be purchased online and is difficult to obtain. The SIPS includes a rating guide with suggested probes and anchors; however, the guide provides minimal guidance on making negative symptom ratings and there are no standardized gold-standard training videos and associated rating explanations that can be freely used to establish inter-rater reliability within and between groups. While training materials for the CAARMS are easy to acquire online, training is not freely available, and like SIPS training, cost may be prohibitive for some. While the CAARMS training materials include a DVD along with a manual that incorporates training vignettes, the training DVDs contain interviews with individuals acting out symptom portrayals, rather than actual CHR cases (Nelson et al., 2008). Such procedures may not translate easily to becoming reliable in rating negative symptoms as they occur in CHR participants. Finally, although gold standard ratings are established for the training vignettes, these vignettes were written to contain all of the information necessary to rate the scales and may not approximate information procured through an actual interview (Nelson et al., 2008). The development of adequate and accessible training materials is critical for not only establishing reliability within individual research groups, but also across studies conducted throughout the field.

Issues with Adapting Scales Designed for Adults with Psychotic Disorders:

There are also issues associated with adapting existing scales designed for adults with diagnosable psychotic disorders to the CHR population. The CAINS (Gur et al., 2015) and BNSS (Strauss & Chapman, 2018) were both recently adapted for use in CHR youth. The

adaptations focused on revising item probes (i.e., questions used in the interview) to make them more applicable to CHR youth, but did not modify item anchors that are used to make ratings. Psychometric analyses of the revised scales indicated that the adaptations were suboptimal for a CHR population- mean item scores approached floor, item and subscale scores were highly positively skewed, and subscales showed modest to weak convergent and discriminant validity with external validators. Suboptimal psychometrics likely reflect a problem inherent to the process of adaptation itself- the CAINS and BNSS anchors were not modified and the scales were still designed to evaluate symptoms in the range commonly observed in patient populations. The subtleties of negative symptoms at the lower end of the continuum were not covered, thereby restricting range and affecting psychometrics. Similar issues would affect attempts to modify any other existing negative symptom scales designed for adults with psychotic disorders. New scales that are designed specifically for CHR youth are therefore clearly needed.

Toward the Next-Generation of Negative Symptom Assessment in CHR Youth:

The NIMH consensus conference recommended the development of new, next-generation rating scales that overcome limitations of existing scales described above (Kirkpatrick et al., 2006). To extend these recommendations to a critical population, youth at CHR for psychosis, the Prodromal Inventory for Negative Symptoms (PINS) was developed (Pelletier-Baldelli et al., 2017). An initial study evaluated the psychometric properties of the PINS in 53 CHR cases, 30 of whom were re-evaluated at 12-months (Pelletier-Baldelli et al., 2017). Results indicated that the PINS demonstrated adequate internal consistency, inter-rater reliability, convergent validity, and discriminant validity. Although the PINS was modeled after existing next-generation measures developed for the chronic phase of schizophrenia, psychometric issues existed and the anhedonia, avolition, and asociality items were not comprehensive enough to capture the range of hedonic, social, or goal-directed activities that occur in adolescence.

To address these issues, a comprehensive 2nd generation measure was developed by the laboratories of Drs. Gregory Strauss and Vijay Mittal, called the Negative Symptom Inventory-Psychosis Risk (NSI-PR). The scale was designed to comprehensively cover the 5 domains from the 2005 consensus meeting, while accounting for conceptual and psychometric issues that were observed on the PINS. The NSI-PR was designed specifically to target CHR youth, taking into account aspects of behavior and socialization that are common to this age range. Asociality items evaluate social media/texting behavior and avolition is evaluated for role (e.g., school) and recreational activities common to youths. An attempt to isolate primary negative symptoms was undertaken by defining constructs of interest in the manual, precise anchors, and probes that avoid focusing on secondary confounds. Secondary negative symptoms can also be identified via separate items for inner-experience and behavior for asociality and avolition, and the use of discrepancy scores that suggest secondary contributions when discrepancy is high (Strauss et al., 2012). Based on contemporary affective science, the anhedonia domain includes separate items for anticipatory pleasure and past-week pleasure (frequency and intensity) in relation to

recreational, role, social, and physical activities. These items rate intensity of anticipated and remembered pleasure, as well as frequency of past week pleasure, because the CHR population appears to be characterized by a genuine deficit in hedonic capacity (Jhung et al., 2016; Schlosser et al., 2014; Strauss et al., 2018) (see Table 3). A one-week timeframe was adopted to address confounds resulting from cognitive impairment that affect retrospective interviews using lengthier timeframes (Strauss & Gold, 2012).

A multi-site psychometric study is currently in progress to validate the NSI-PR and derive a final version of the scale in the labs of Drs. Strauss, Mittal, and Walker. The approach to scale development adheres to the process agreed upon in the NIMH consensus conference that was used to develop the CAINS for use in schizophrenia (Horan et al., 2011; Kring et al., 2013). This involves taking a broad, overly inclusive approach to developing items, which can later be trimmed via an iterative, data-driven process across sequential studies. The end product will be a next-generation negative symptom scale designed specifically for use with CHR youth that was derived based on empirical considerations, rather than subjective clinical impression. By engaging in this iterative approach to scale development across multiple sites, we will ensure generalizability of the NSI-PR to the types of large-scale, multi-site CHR laboratory and treatment studies that are required to obtain sufficient sample sizes to examine conversion to psychosis (e.g., NAPLS). Standardized interview (manual), rating (workbook, scoresheet), and training (gold standard interview videos and ratings) materials are being developed to facilitate use of the NSI-PR in multi-site studies. Item anchors and scaling are being validated using novel approaches to sampling real-world behavior (e.g., automated facial analysis, ecological momentary assessment, social media use). To determine whether the NSI-PR offers advantages over the SIPS in terms of predicting clinically relevant outcomes, participants will be followed longitudinally and re-evaluated after 12 months. We are evaluating the hypothesis that relative to the SIPS, the NSI-PR will demonstrate incremental validity by being be a significantly stronger predictor of: A) change in NAPLS Risk Calculator Scores from baseline to 12-months, B) decline in community-based functional outcome from baseline to 12-months.

Conclusions and Future Directions

Much like schizophrenia, APS is a clinical syndrome characterized by heterogeneous clinical presentations (Addington et al., 2011). Although negative symptoms are often the most disabling/persistent component of the syndrome and the most relevant to functional outcome, they have received relatively little empirical attention in this population. Studies using first-generation scales (e.g., SIPS, CAARMS, SPI) have led to important advances regarding the phenomenology, course, and pathophysiology of negative symptoms in CHR; however, due to conceptual and methodological limitations of these scales, it is unclear whether conclusions are confounded or more granular implications have been missed. Given that negative symptoms can result from multiple psychological and biological mechanisms (i.e., equifinality) (Strauss & Cohen, 2017), it is paramount that new scales be developed that assess the construct with enough precision to disentangle processes unique to negative versus other symptoms (e.g., positive, disorganized). Initial attempts to address this need in the field focused on adapting scales designed for schizophrenia (Strauss & Chapman, 2018; Gur et al., 2015); however, the adaptations were not ideal. Measures designed specifically

for the unique needs of CHR youth are needed. Such a measure was recently developed, the PINS (Pelletier-Baldelli et al., 2017), but it too had conceptual and methodological issues. To make significant advances in the early identification and prevention of psychosis, it will be critical to continue making progress in optimizing assessment strategies for CHR youth, a process now being undertaken with the NSIPR. This measure is now being used in several large, multi-site collaborative CHR projects (e.g., Computerized Assessment of Psychosis Risk-CAPR; Psychosis Risk Outcomes Network ProNet) that are adopting a hybrid assessment strategy that combines the advantages of the SIPS for measuring positive and general symptoms and the NSI-PR for negative symptoms.

Finally, rating scales represent but one approach to negative symptom assessment. It is now possible to perform automated analysis of speech and voice from video-recorded interviews or data collected during real-world contexts via digital phenotyping (Cohen et al., 2019). These may serve as promising objective measures of blunted affect and alogia (Cohen et al., in press). Additionally, mobile phones and smart bands can be used to obtain subjective (e.g., ecological momentary assessment self reports) and objective digital phenotyping measures of avolition, asociality, and anhedonia (e.g., accelerometry, geolocation) (Depp et al., 2020). The promise of these technological advances has yet to be realized or psychometrically evaluated in CHR. However, they may hold promise for validating and refining existing clinical rating scales, or to serve as measures of negative symptoms in and of themselves. Future studies should evaluate the level of compliance, tolerability, and validity of digital phenotyping based approaches to negative symptom assessment in CHR youth in relation to clinical rating scales. These approaches may reflect the third generation of negative symptom assessment, with significant promise for use in a clinical group that makes regular use of mobile devices in daily life.

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Table 1.

Conceptual Limitations of Currently Existing UHR Interviews with Regard to Negative Symptom Assessment

Conceptual Limitations				
Negative Symptom Domains				
Avolition	*Asociality*	*Anhedonia*	*Blunted Affect*	*Alogia*
SIPS				
• Separate experiential and objective components not measured. • Occupational functioning item is not part of the negative symptom construct	• Does not contain an asociality item specifically. • Asociality conflated with anhedonia. • Does not measure social interactions that take place via social media and texting.	• Anhedonia item evaluates social domain only and neglects physical, role, or recreational domains. • Conflates asociality, social anxiety, and social skill. • Probes do not evaluate pleasure for social situations. • Does not differentiate between anticipation and consumption of pleasure or frequency vs. intensity of pleasure.	• Expression of Emotion item does not separate channels of communication (face, body, voice). • Conflates alogia and blunted affect. • Incorporates poor rapport and lack of eye contact into rating, which are not part of the construct	• Expression of Emotion item conflates blunted affect and alogia. • Conflates poor rapport
CAARMS				
• Items do not incorporate persistence, only initiation. • The impetus for the activity is also not considered (i.e., whether the subject had to be pushed to initiate the activity)	• Does not contain a formal asociality item contained within the subheading of negative symptoms. • The social isolation item is the closest to asociality, but it conflated with social anxiety. • Does not evaluate social media, texting etc.	• Assesses interest, which is typically linked to depression rather than schizophrenia-spectrum disorders. • The subjective emotional experience item includes elements of inappropriate affect, which is more conceptually relevant to disorganization and incorporates information on experience of both positive and negative	• Factors in rater rapport, rather than pure behavioral observation. • Not a comprehensive evaluation of face, voice, and body gestures	• Conflated with disorganization including content related to thought blocking and vagueness. • Incorporates both participant self report and observed speech behavior, despite issues with insight affecting self-report

Conceptual Limitations					
			emotion reductions		
			SPI		
• Items focus solely on internal experience of avolition (including motivation, initiation, and persistence), but neglect behavioral engagement in goal-oriented tasks.	• Contains 1 item inquiring into desire for social contact. • Does not evaluate nature, quality, and frequency of social engagement. • Neglects interactions on social media, texting etc.	• Minor reference to decreased positive emotional response toward others. • Does not assess for hedonic behavioral experience of any sort. • Does not contain items assessing physical, role, or recreational hedonic experience, nor any reference to anticipatory or past frequency of enjoyment in activities.	• Items prioritize self-report over behavior.	• Items prioritize self-report over behavior.	

Table 2.

Methodological Limitations of Currently Existing UHR Interviews with Regard to Negative Symptom Assessment

Methodological Limitations		
Development	*Structure/Psychometrics*	*Training/Administration*
	SIPS	
• Scale development based on one group/university, clinical observation, small and unrepresentative sample, and symptom presentation in a psychotic population.	• Single items assess entire domains of negative symptomatology, scaling is imprecise. • Scale structure neglects details and nuances that are meaningful in psychosis-risk populations, and generates skewed data. • Problems with subscale items prevent factors from mapping onto motivation/ pleasure and emotional expression factors as they are understood in chronic schizophrenia; item removal may be warranted. • Items not part of the negative symptom construct are included.	• Training is not freely available and cost may be prohibitive for some. • No standardized gold-standard rating videos are available • Process of establishing reliability is arduous.
	CAARMS	
• CAARMS cutoffs for identifying CHR individuals based on the BPRS and CASH, which are known to not measure all negative symptom constructs as defined in the NIMH consensus conference (Kirkpatrick et al., 2006).	• Unclear whether the sample was demographically diverse or representative of the broader CHR population (Yung et al., 2005). • Predictive validity of negative symptom items may not be clinically meaningful (Yung et al., 2005). • Concurrent validity was assessed using the BPRS and CASH, which are based on outdated conceptualizations of negative symptoms. • No studies have been done to examine the separate negative symptom psychometrics of the CAARMS. • Structure of negative symptom items unclear. • Single items used to assess domains of symptoms. • Scaling is imprecise.	• Training is not freely available and cost may be prohibitive for some. • A training DVD is available along with a manual that incorporates training vignettes, but the training DVDs contain interviews with staff members acting as though they are individuals with CHR symptoms rather than actual individuals with the symptoms in question. • Gold standard ratings are established for the training vignettes, which are written to contain all of the information necessary to rate the scales and may not approximate information procured in an actual interview.
	SPI	
• Although SPI items were derived from cluster and facet analyses on prodromal youth and individuals diagnosed with schizophrenia, content was not developed with negative symptomatology in mind.	• The measure does not assess for negative symptoms specifically. • Structure of items relevant to negative symptom construct is unclear. • There is no negative symptom domain or total score. • The closest domain is “adynamia” that includes items related to avolition, with additional items under various other	• Interview and instructions must be purchased online. • No training videos or tools available.

Methodological Limitations			
•	The primary goal of the SPI is to assess for basic symptoms.	Basic Symptom domains within the scale. • Ratings are based solely off internal experience, rather than overt behavior.	

Table 3.

Addressing Existing Scale Limitations with the Negative Symptom Inventory Psychosis-Risk (NSI-PR)

Existing Scale Limitations	Initial Steps to Address Limitation in NSI-PR
	Addressing Conceptual Limitations
(1) Inclusion of items based on outdated conceptualizations and failure to cover the 5 domains identified in the 2005 NIMH consensus conference	• Evaluates the 5 NIMH consensus domains • Addresses item conflation by ensuring asociality, avolition, anhedonia, blunted affect, and alogia are distinct – Alogia not conflated with disorganized speech – Social anhedonia and asociality separated – Asociality does not emphasize discomfort around others, which can emphasize anxiety • Examines anhedonia across variety of domains (social, role, physical, and recreation) • Rates blunted affect from multiple channels including gestural (shoulders, trunk, hands, head), vocal, and facial expression • Anhedonia assessment consistent with schizophrenia-spectrum research and does not emphasize interest in pleasurable activity, only anticipation and consumption
(2) Experiential and objective components not separated for asociality and avolition	• Asociality and avolition have distinct items evaluating internal experience and behavior • Internal experience ratings identify the individual's motivation, desire, and significance placed on activity • Behavioral ratings identify the observable actions, planning or organizing done in relation to role or recreation (avolition) or social activity (asociality)
(3) Current anhedonia research not incorporated	• Items differentiate between anticipatory and consummatory components of hedonic experience • Anticipation is evaluated through affective forecasting (thinking about future enjoyment, how good does one think they will feel) • Consummatory is evaluated through past week intensity • Past week frequency of pleasurable activity is also assessed for the behavioral component of anhedonia
(4) Failure to consider primary versus secondary negative symptoms	• Scale structure allows for examination of the influence of secondary factors on symptom expression in multiple ways: – Item anchors and probes designed to focus on factors relevant to primary negative symptoms (e.g., apathy), rather than secondary negative symptoms (e.g., depression, anxiety, paranoia) – The differentiation between internal experience and behavior can inform whether anxiety, loneliness, or apathy is present and to index influences of secondary negative symptoms on avolition and asociality (Strauss et al., 2012) – The novel lack of distress item, is a key factor in identifying primary negative symptoms (Kirkpatrick et al., 2001)
(5) Limited coverage of adolescent/early adulthood motivational and social problems	• Emphasis on conceptualizing role of social media use, texting, and gaming on items • Inclusion of chores and hygiene in role items to account for lack of work or school in holiday or summer schedules for this age group • Preliminary evidence indicates full range is endorsed on items – reflecting increased accuracy of capturing age-appropriate range of experience.
	Addressing Methodological Limitations
(1) Scale Development	• Developed based on guidelines form the NIMH consensus meeting suggesting use of an iterative, data-driven approach • Initial broad inclusion of items to be further honed in empirical analysis.

Existing Scale Limitations	Initial Steps to Address Limitation in NSI-PR
	• Currently in the process of undergoing a large-scale evaluation to conduct the multiple iterative assessment of scale items.
	• Use of automated facial analysis, ecological momentary assessment, , and evaluation of social media use are being examined to aid in evaluation of item validity and refinement.
	• Assessing a demographically representative sample of individuals in a wide age range of the prodromal syndrome
(2) Psychometric Limitations	• Preliminary psychometrics indicate good internal consistency, inter-rater reliability, convergent and discriminant validity.
	• Limitations with positive skew and comprehensiveness of items (particularly anhedonia, avolition, and asociality) have been addressed and may be further improved with subsequent iterations of the scale
	• Anchors in the NSI-PR were designed with a full range of adolescent/young adult experience in mind
	• Multiple items assess the 5 domains
(3) Limited Training Materials	• Current training includes on-site or virtual meeting overview, description of the scale, common pitfalls, suggestions for ratings, vignettes.
	• Ongoing availability of scale developers to address questions, concerns, or issues that may arise with scale use.
	• Gold-standard training videos and ratings have been developed