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Reconsidering the Latent Structure of Negative Symptoms in Schizophrenia: A Review of Evidence Supporting the 5 Consensus Domains

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Negative symptoms have featured prominently as a core symptom of schizophrenia (SZ) since the earliest descriptions of the disorder.[1,2] They predict a range of poor clinical outcomes, such as reduced rates of recovery,[3] poor functional outcome,[4] lower subjective well-being,[5] and liability for the onset of a psychotic disorder.[6] Unfortunately, interventions targeting negative symptoms have produced minimal benefits and no drug has received US Food and Drug Administration approval for an indication of negative symptoms.[7]

A factor likely to have contributed to the limited progress in developing effective treatments is that there is a lack of conceptual clarity regarding the latent structure of negative symptoms. Latent structure refers to how the universe of behaviors that comprise negative symptoms relate to underlying traits, factors, or domains. Practically, it indicates how many aspects of negative symptoms should be targeted by psychometrically sound clinical rating scales and diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and *International Classification of Diseases*. The following review contends that contrary to the currently held convention, negative symptoms comprise 5 central domains. These domains are missed by most rating scales—in part because of their limited item coverage and the methodological shortcomings of previous attempts to decipher such domains.

Factor analysis is the most commonly used method for describing the latent structure of a construct. Early factor analytic studies correctly indicated that negative symptoms are a dimension of psychopathology that is separate from positive and disorganized symptoms.[8–10] However, the same studies erroneously concluded that negative symptoms are a unidimensional construct, having obtained and analyzed ratings of negative symptoms and other symptoms of SZ in 1 analysis. The inclusion of negative symptom items along with items from other constructs causes negative symptom items to artificially aggregate together, making the construct arbitrarily seem unidimensional. When exploratory factor analysis (EFA) was applied to items within negative symptom scales only, evidence for 2 distinct dimensions emerged across a range of scales.[11–18] These dimensions reflect diminished motivation and pleasure (MAP: anhedonia, avolition, asociality) and diminished expressivity (EXP: blunted affect, alogia). These findings led the field to shift away from a unidimensional conceptualization, in favor of a 2-dimensional conceptualization of negative symptoms.[19] EFA studies supporting the 2 factors have been influential, informing how researchers search for pathophysiological mechanisms of negative symptoms[20–24] and how pharmaceutical companies approach targeted treatment development.[25]

However, conclusions about the latent structure of negative symptoms based on EFAs alone are insufficient. EFA is a data reduction technique that infers the presence of latent traits or factors responsible for shared variance among a set of items. It does not specify an underlying structure but rather assumes that each item could be related to each latent factor. Exploratory factor analyses are important for generating hypotheses regarding the latent structure of negative symptoms; however, these analyses are not capable of actually testing competing models regarding the number of dimensions that exist within the negative symptom construct. They are also uninformative about how factors extracted actually fit the data.

Confirmatory factor analysis (CFA) is a statistical approach that enables definitive conclusions regarding latent structure by objectively comparing a priori models based on theory. Few CFAs have been conducted on negative symptom scales. CFAs of the Scale for the Assessment of Negative Symptoms (SANS)[26] were

conducted; however, these included items no longer considered part of the negative symptom construct (eg, inappropriate affect, inattention),[27,28] limiting conclusions about the latent structure of negative symptoms. Only 2 CFA studies have examined competing models for scales including items based on modern conceptualizations. Strauss et al.[29] used CFA to evaluate the latent structure of the SANS (n = 268),[26] Brief Negative Symptom Scale (BNSS)[30] (n = 192), and Clinical Assessment Inventory for Negative Symptoms (CAINS)[17] (n = 400). Four CFA models were compared. The first model was unidimensional, which considered whether all items best reflect a single latent negative symptom construct. The second model evaluated the 2-dimensional model identified in prior EFA studies,[11–18] reflecting EXP and MAP factors. The third model was a 5-factor model that specified 1 factor for each of the 5 domains identified in the 2005 National Institute of Mental Health (NIMH) consensus development conference[31]: anhedonia, avolition, asociality, blunted affect, and alogia. The fourth model was a hierarchical model with 2 second-order factors reflecting EXP and MAP, as well as 5 first-order factors reflecting the 5 consensus domains. Results were consistent across the SANS, BNSS, and CAINS. The 1- and 2-factor models provided poor fit for the data. The 5-factor and hierarchical models provided excellent fit, with the 5-factor model slightly outperforming the hierarchical model. The consistency of these findings across the 3 scales suggests that it is not something about the organization of the scale, manual, worksheet etc. that arbitrarily produces the 5-factor structure because these elements are very different across measures.

In a follow-up CFA study, Ahmed et al.[32] evaluated the 4 aforementioned factor models across 5 cross-cultural sample on the BNSS, with a total number of 1691 [Italy (n = 937), Spain (n = 115), China (n = 163), Switzerland (n = 119), and the United States (n = 357)]. Results replicated Strauss et al.,[29] indicating that 1- and 2-factor models provided poor fit for the fata, but 5-factor and hierarchical models provided excellent fit. Again, the 5-factor model slightly outperformed the hierarchical model.

Given that CFA can underestimate the number of factors when the correlations between factors are high and when sample size is small, Strauss et al.[33] examined whether the 5-factor structure was observed using an alternate mathematical approach, ie, not subject to these limitations: network analysis. Specifically, a community detection network was evaluated for the BNSS in an American sample (n = 201) and an Italian sample (n = 912) to determine how different subsets of nodes (ie, BNSS items) in the network were connected to each other (ie, whether they have a stronger connection with each other while having a weaker connection with the nodes in other communities). Similar to the CFA, network analysis also identified the 5 domains as separate communities.

Collectively, results of 3 recent articles,[29,32,33] which had a total number of 3695, suggest that 1- and 2 (MAP, EXP)-dimensional models of negative symptoms do not adequately capture the complexity of the negative symptom construct. Importantly, support for the hierarchical model[26,31] should not be taken as further evidence for conceptualizing negative symptoms primarily around the MAP and EXP dimensions. This is because MAP and EXP are secondary dimensions in these hierarchical models and the 5 factors are primary. Because primary dimensions are the ones directly influencing ratings of all negative symptoms in these hierarchical models, this suggests that the 5 domains, not the MAP/EXP dimensions, are most fundamental and best account for negative symptom structure. The 5 domains identified in these models reflect the consensus domains identified in the 2005 NIMH development conference[31]: anhedonia, avolition, asociality, blunted affect, and alogia. These conclusions regarding latent structure are not scale dependent (the 5-domain model was supported in the SANS, BNSS, and CAINS), culturally restricted (the 5 domains were observed across 5 diverse cultures/languages), or specific to a singular mathematical approach (the 5 domains were found using CFA and network analysis).

This reconceptualization of the latent structure of negative symptoms has several important implications:

1. Based primarily on prior EFA results,[11–18] the *DSM-5* structured its description of negative symptoms around the 2 broad MAP and EXP dimensions. If future studies provide support for unique external validators that predict the 5 domains, each of the domains should be considered separately within the diagnosis because they reflect separate aspects of psychopathology.
2. Current procedures for scoring negative symptom scales as a singular total score or MAP/EXP dimension scores on the CAINS, BNSS, and SANS are inadequate. Strong fits for the hierarchical models in Strauss et al.[29] and Ahmed et al.[32] suggest that the MAP and EXP dimensions are not irrelevant; however, the 5 domain scores should also be calculated and considered a more fundamental/base aspect of negative symptoms for which scores should be derived. Strauss et al.[29] suggested guidelines for calculating scores for the 5 domains on the SANS, CAINS, and BNSS.
3. Treatments may have differential efficacy for these 5 domains. Failing to evaluate the 5 domains separately may prevent observation of meaningful treatment effects that are domain specific, rather than tied to the 2 broader dimensions. It is possible that trials already conducted have observed positive treatment effects, but such effects were masked by the calculation of scores that lack appropriate granularity. Reanalysis of past studies may be warranted and future treatment trials should calculate scores for each of the 5

domains, rather than a global total score or MAP and EXP dimensional scores alone. Indeed, there is evidence for differential effects of treatments on some of the 5 domains, but not others (eg, Kirkpatrick et al.[34]).

4. Pathophysiological mechanisms specific to the 5 consensus domains are likely being overlooked because the negative symptom construct is not examined with enough granularity. As a result, progress in identifying novel treatment targets has been slow and ineffective.[7] There are currently no overarching guidelines for how to map pathophysiological mechanisms onto the 5 domains. The NIMH RDoC initiative is one approach that has potential for making progress in identifying mechanisms underlying each domain. The RDoC has delineated neurobiological processes associated with aspects of "positive valence systems" and "social processes" that are conceptually related to the 5 negative symptom domains. Using such a framework, pathophysiological mechanisms associated with each domain could be evaluated to promote targeted treatment development.

In table 1, we provide a hypothetical mapping of the 5 domains onto RDoC constructs, as an example for how researchers might go about making progress in examining mechanisms related to each domain. Some of the paradigms listed in the table (eg, progressive ratio task as a measure of effort–cost computation) have been translated to human platforms and validated for use with clinical populations (eg, Grant et al.,[35] Treadway et al.,[36] and Bismark et al.[37]). However, the majority of basic neuroscience paradigms that measure constructs relevant to the 5 domains do not have a human analogue. The generation and translation of such tasks represents and urgent need for the field. Such tasks may represent intermediate phenotypes that are more closely linked to the pathophysiology of each negative symptom domain than clinical ratings. These paradigms may be more likely to produce valid treatment changes than clinical rating scales because they are closer to the underlying mechanism. However, extensive work on the psychometrics of such tasks, development of alternate versions, and validation at circuit and behavioral levels is needed before these tasks can be adopted for use in clinical trials. Note that few studies have taken an approach such as the one outlined in table 1, likely because common conventions in conceptualizing negative symptoms as 1 or 2 dimensions led the field to believe that such granularity was unnecessary. The links presented in table 1 are hypothetical and used only to illustrate a potential approach that could be fruitful, not to document known associations. Among the few studies that have explored the correlates of individual domains, results are inconsistent, suggesting a need for further research that takes an RDoC type approach. Future studies should also evaluate the role of primary vs secondary[38] negative symptoms when exploring pathophysiological mechanisms of the 5 domains, because this may account for heterogeneity and inconsistencies among studies.

Demonstrating external validity of the 5 domains will be a critical next step for the field. We recommend a multitiered process. First, it may be beneficial to reanalyze existing datasets that contain a modern negative symptom rating scale capable of assessing the 5 domains (ie, CAINS, BNSS) and other variables that have been shown to have correlations with negative symptoms in past studies (eg, MRS, structural MRI, functional MRI, DTI, genes, RNA, cytokines, cognition, functional outcome, premorbid adjustment, summer season of birth). Correlations should be examined with the 2 broad MAP/EXP dimensions, as well as the 5 consensus domains. Such data mining would provide insight needed to generate specific hypotheses for new studies designed to systematically examine external validity. It is likely that some external variables will map onto a 2-dimensional MAP/EXP structure, whereas others will show unique correlates with the 5 domains that are masked by the 2 broader dimensions. Because psychometric studies are needed to validate translational tasks, progress toward identifying unique correlates of the 5 domains and 2 dimensions may be slow.

In conclusion, the current review highlights evidence indicating that a paradigm shift in the way the field views the latent structure of negative symptoms may be warranted. Although the 2-dimensional model (MAP/EXP) has gained traction over the past decade, this conceptualization is not fully statistically or theoretically justified. New evidence suggests that a 5-domain conceptualization is statistically and theoretically justified. Adopting this 5-domain structure has important practical and theoretical implications. Future research on the pathophysiological mechanisms underlying the 5 domains is needed. If this research indicates distinct mechanism associated with the 5 domains, then a shift in *DSM* diagnostic procedures and the approach to targeted treatment development may be warranted.

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Table 1. RDoC Constructs Mapped Onto the Individual Negative Symptom Domains

Negative Symptom Domain	RDoC System	RDoC Subconstruct	Paradigms	Brain Structures/Circuits
Avolition	Positive Valence	Reward Valuation: Delay	Delay discounting	Anterior medial OFC; mPFC; ventral tegmental area/ substantia nigra
Avolition	Positive Valence	Reward Valuation: Effort	Effort Expenditure for Reward; Progressive Ratio, Cognitive Effort Task	Basolateral amygdala; dorsal ACC; ventral pallidum; ventral striatum; VTA
Avolition	Positive Valence	Reward Anticipation	Monetary Incentive Delay task response to reward predictive cues	VTA; ventral striatum
Avolition	Positive Valence	Probabilistic and Reinforcement Learning	Drifting double bandit; Pavlovian conditioning; Probabilistic Stimulus Selection Task	Amygdala; dorsal striatum; medial PFC; OFC; ventral striatum; VTA
Avolition	Positive Valence	Reward Prediction Error	Drifting Double Bandit; Routledge Passive Lottery Task	VTA; NAcc
Anhedonia	Positive Valence	Initial Response to Reward	Sweet taste test; response to pleasant laboratory-based stimuli (eg, photographs, sounds, words); Monetary Incentive Delay Task response to reward outcomes	Anterior insula; dorsal ACC; lateral hypothalamus; medial OFC; nucleus accumbens; ventral pallidum; ventromedial PFC; VTA
Asociality	Social Processes	Affiliation and Attachment	Cyberball; One-armed Bandit Task	Amygdala; fusiform facial gyrus; NAcc; OFC; PVN; VMPFC; VTA-NAcc-VP-amygdala
Blunted Affect	Social Processes	Production of Facial Communication	Tasks that induce emotion by presenting a pleasant stimulus and recording facial expression, decoded via behavioral observation, electromyography, or computerized analysis	PAG; AC
Blunted Affect, Alogia	Social Processes	Production of Non-Facial Communication,	Tasks that induce emotion by presenting a pleasant stimulus and recording vocal or body gesture behavior, decoded via behavioral observation, electromyography, or computerized analysis; production of speech	R-IFG-RSTG

Note: OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; VTA, ventral tegmental area; PFC, prefrontal cortex; CRF, corticotrophin releasing factor; NAcc, nucleus accumbens; PVN, periventricular nucleus; VMPFC, ventromedial prefrontal cortex; VP, ventral pallidum; R-IFG-RSTG, Right inferior frontal gyrus–right superior temporal gyrus.

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