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Viewpoint

Assessment and the concept of negative symptoms

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Negative symptoms, which consist of a decrease or loss of normal psychological behaviour or function, are core aspects of schizophrenia. The American Psychiatric Association's Fifth Edition of the Diagnostic and Statistical Manual includes negative symptoms in the diagnostic criteria for schizophrenia. These deficits decrease quality of life and function in people who have them, and even with improvement in positive psychotic symptoms, depression, and anxiety, many people with schizophrenia continue to endure debilitating negative symptoms. The Consensus Development Conference sponsored by the US National Institute of Mental Health (NIMH) concluded negative symptoms include blunted affect, alogia, asociality, anhedonia, and avolition, while noting other features may be included in the concept in the future.[1]

Viewing negative symptoms through the lens of assessment illuminates the evolving landscape of this research field. To appreciate current assessment tools, a historical overview of the concept and its assessment is required.

The nineteenth century: avolition

During the nineteenth century, researchers focused on the negative symptom of avolition. In the first half of the century, Wilhelm Griesinger noted, "*dullness and weakness of all physical reaction – in an absence of sentiment, indifference and diminished energy of the will*" were found in some patients with psychosis.[2] Emil Kraepelin, influenced by Griesinger, expanded upon this in his description on dementia praecox, noting a weakening of emotional activities that propel action. Neither proposed a structured method of assessment, nor did either one suggest avolition was a marker of a subgroup within psychotic disorders.

John Hughlings Jackson and John Russell Reynolds developed the concept of negative symptoms found in neurological patients. Reynolds defined negative symptoms as the negation of a function; examples include paralysis and anaesthesia. Jackson postulated an interaction of positive and negative symptoms but neither concerned themselves with negative symptoms within psychiatric disorders or developed a quantitative assessment.[3]

Twentieth century: measuring symptoms

In the first half of the twentieth century, another specific negative symptom emerged because of a focus on theory and research. Rado in 1953 and Meehl in 1962 proposed that anhedonia, a decreased ability to experience pleasure, contributed to the aetiology of schizophrenia, but neither one developed a measurement tool. Maurice Lorr was a pioneer in developing scales for psychotic disorders. In 1962, Overall and Gorham published the Brief Psychiatric Rating Scale (BPRS), a 16 to 18-item scale that was based on Lorr's scales. Five factors – groups of scale items that have scores that correlate with each other – were identified, including a negative symptom factor. As the BPRS had other factors such as one for positive psychotic symptoms, it became widely used in studies of psychotic disorders. One of its limitations was that it failed to distinguish signs (observable by others) and symptoms (internal experience.) The original version also lacked anchors, which are guides describing the level of severity for each item score.

In 1974, Strauss et al., reviewing the results of the International Pilot Study of Schizophrenia (IPSS), proposed a categorization of symptoms into three groups: positive symptoms, negative symptoms, and disorders of relating.[4] In 1976 the Chapmans published the first quantitative tool for the assessment of negative symptoms, their social and physical anhedonia scales. Timothy Crow was the first to propose negative symptoms could be used to define a biological subgroup with schizophrenia.[5] He proposed two subtypes, Type I and Type II schizophrenia, the latter characterized by poor prognosis and a predominance of cognitive and negative symptoms.

In 1984, Andreasen published the first widely used instrument that measured negative symptoms exclusively, the Scale for the Assessment of Negative Symptoms (SANS).[6] It quantified more symptoms than were found in previous instruments. The SANS was an important step forward, as it facilitated study of negative symptoms as a separate focus of research and treatment. Increasing study of negative symptoms contributed to the eventual development of the concept of transdiagnostic psychopathology. Andreasen also delineated two schizophrenia subtypes, based on SANS scores. The validity of these two groups gained some support but no firm evidence was established.

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The Positive and Negative Syndrome Scale (PANSS) expanded on the items in the BPRS, but also had detailed anchors, which made interrater reliability – the ability of raters to agree on the appropriate score – much easier. The PANSS has become the standard instrument for clinical trials of psychotic disorders in much of the world, although when negative symptoms are the focus of the trial another instrument may become the primary or secondary outcome measure. SANS scores and negative symptoms scores from the PANSS and BPRS scores are highly correlated. However, the PANSS and SANS cover a wider range of symptoms than the BPRS, and the PANSS often has better interrater reliability because of its anchors.[7]

During the 1980s, critics highlighted issues with the existing negative symptom measures. Examination of the factor structure of the scales played an important role in these developments. A consensus developed that the SANS included items that were not negative symptoms but were part of positive symptoms (q.v. disorganization) or cognitive impairment (q.v. attention.) Another problem was that negative symptoms have many causes. For instance, a patient may exhibit asociality because of depression, paranoia, or a lack of interest in relationships. Carpenter et al. argued that primary negative symptoms (PNS), which are part of the illness, should be distinguished from secondary negative symptoms, which are due to other factors such as depression.

The Schedule for the Deficit Syndrome (SDS) was developed to distinguish between patients with and without PNS, leading to substantial research on these two groups. Evidence of differences in symptoms, etiological factors, course of illness, treatment response, and biological correlates has led to the hypothesis that PNS delineate a distinct disease within schizophrenia. However, difficulty of intergroup reliability with the SDS is demonstrated by the failure of many studies to achieve the clinical profile expected for the PNS group. Consequently, to conduct clinical trials focused on negative symptoms that include mainly patients with PNS, it is increasingly common for investigators to use entry criteria that include the presence of minimal positive psychotic symptoms and dysphoria, and moderate to severe negative symptoms. This approach reduces the risk of an ambiguous interpretation of negative symptom improvement, as improvement cannot be attributed to improvement in these other factors.

The current landscape

The NIMH Consensus Development Conference on Negative Symptoms, mentioned above, produced recommendations about assessment tools, regulatory issues, and treatment trial design.[1] One recommendation was creation of a rating scale that included all five consensus domains. Two scales grew out of the Conference, the Brief Negative Symptom Scale (BNSS)[8] and the Clinical Assessment Interview for Negative Symptoms (CAINS),[9] two psychometrically robust tools offering comprehensive coverage of the five recognized negative symptom domains. The BNSS includes an additional domain – lack of normal distress – though its status remains uncertain due to weak psychometrics for that item, which may reflect its relative rarity.

Exploratory factor analyses of these two scales and the SANS usually identified two factors: expressivity (alogia and blunted affect) and another factor that includes avolition, asociality, and anhedonia. Subsequent confirmatory factor analyses, which permit hypothesis testing and facilitate comparison of different factor structures, usually identified factors that correspond to the five consensus domains: alogia, anhedonia, asociality, amotivation, and blunted affect. The Self-Evaluation of Negative Symptoms (SNS) tool, a patient-reported instrument, demonstrated a five-factor structure like that of the CAINS, BNSS, and SANS.

The consistency of these factors across instruments and several languages has important implications. The relative independence of these factors suggest they may have distinct biological underpinnings. If they have separate etiopathophysiologies, analyses based on total negative scale scores in trials may yield false negatives, as a treatment may impact one or two of the factors but not others. This issue is also important in studies of risk factors, biological correlates, etcetera.

Limitations of psychometric scales

Rating scales such as the BNSS and CAINS, although administered by trained raters, are imperfect due to their reliance on participants' memory, self-observation, and a willingness to report symptoms among other factors. These challenges introduce noise into measurements. Digital biomarkers, which are generated using smartphones and wearable devices for real-time, active and passive data collection, may mitigate these problems.[10] The field is now working to understand the meaning of the many novel digital measures, such as geolocation, accelerometry, and ambient sound.

Moreover, negative symptoms, positive symptoms, anxiety, and other aspects of psychopathology are "transdiagnostic," that is, they are found in a variety of disorders. An increasingly common research strategy is to examine these features across disorders. Often this approach is based on the concepts of the Research Domain Criteria (RDoC) of the US NIMH.[11] The RDoC system is based on the concept that examination of specific signs and symptoms are more likely to reflect specific circuits; animal analogues of these signs and symptoms are part of this approach. The hope is that separating these features for research purposes will facilitate the development of treatments.

Future

Rating methods and negative symptom concepts in schizophrenia have co-evolved. Current measures, such as the BNSS, CAINS, and to some extent, the SANS, offer some agreement on the psychometrics of negative symptoms, although they are not wholly interchangeable. As shown by the results of recent factor analyses, assessment development can have important implications for both the development of concepts of psychopathology and research strategies. With increasing research, the current scales may soon become outdated, while digital phenotyping may offer measures closer to the aetiology and pathophysiology of clinical problems. As measurement remains pivotal in research and clinical care, negative symptom assessments and concepts will continue to co-evolve.

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Conflict of interests

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BK is CEO and part owner of Quantic Innovations (QI), which provides services related to digital phenotyping of people with psychiatric disorders. QI has contracts with Karuna Therapeutics and Sunovion. He receives licensing royalties from ProPhase for use

of the Brief Negative Symptom Scale (BNSS) by for-profit groups; these fees are donated to the Brain and Behavior Research Foundation. In the last three years he has also received honoraria and travel support from ProPhase for training pharmaceutical company raters on the BNSS; consulting fees and/or travel support from Lundbeck, Acadia, ProPhase, Otsuka, and Minerva Neurosciences; fees from anonymized investors through Guideposts and Decision Resources Group; and an honorarium from Otsuka for preparation of educational materials.

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