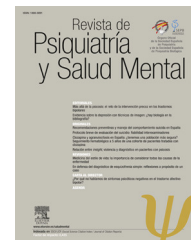




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EDITORIAL

The new challenge in identifying the negative syndrome of schizophrenia[☆]

Ante el nuevo reto de identificar el síndrome negativo de la esquizofrenia

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In 2006 the NIMH proposed a Consensus Statement on Negative Symptoms¹ to develop knowledge of the negative dimension of schizophrenia, using a strategy similar to that of the MATRICS project.² The consensus (1) established and defined the negative symptoms of schizophrenia, (2) emphasised its situation as a treatment necessity not covered and (3) strongly recommended developing new assessment measures that would solve the significant limitations of the already-existing ones. Since that time, it is accepted that the negative symptoms of schizophrenia are as follows: Social Isolation, Anhedonia, Avolition, Flat affect and Alogia.^{1,3}

Apparently there is nothing new under the sun. Back in 1980, T. Crow classified schizophrenia into subtypes I and II based on the predominant symptom, positive or productive as against negative or deficit.⁴ In doing so, he again took up the distinction between positive and negative symptoms that De Clérumbault had introduced into the world of psychiatry in 1942 without much success.⁵ The negative symptoms Crow described were: flattening or blunting of affect, poverty of speech (alogia) or of content, blocking, limited self-care, loss of motivation, anhedonia and social withdrawal. It might be thought that after 25 years of schizophrenia research, the negative syndrome remains anchored in the past, with the same limitations and conceptual difficulties. Although there are still inadequacies,

significant advances have taken place in the conceptualisation and differentiation between this dimension and the rest of the dimensions in schizophrenia.

On the one hand, the distinction between primary and secondary negative symptoms^{6,7} has made it possible to limit more surely what the nuclear symptoms are in negative syndrome. It has also stimulated doctors to identify and treat secondary negative symptoms. On the other hand, the distinction of anhedonia between anticipatory (more characteristic of schizophrenia and related to lack of motivation and behaviour aimed towards an object) and consummatory or experiential (more characteristic of depression)^{8,9} has helped to improve our understanding and assessment of this symptom in the context of schizophrenia. Likewise, this distinction has helped to strengthen the limits between the affective and negative dimensions. Recently, the negative dimension has been split into 2 subdimensions¹⁰: the experiential or being involved in the environment (asociality, anhedonia and avolition) against the expressive (flattening of affect and alogia). This division has helped to explore in greater detail both the concept and psychometric assessment.

One of the greatest difficulties in the conceptualisation of this dimension is the borderline between the negative and cognitive dimensions, a point that is still being debated. It is generally accepted that these 2 dimensions do present similar characteristics with respect to prevalence, difficulty in assessment, progression, prognostic implications and lack of effective treatments. However, it is also accepted that they constitute 2 dimensions that are independent but interrelated. This interrelation is based on the symptoms included in the negative dimension and also on the definition of these symptoms that is adopted.¹¹

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Bearing all of this in mind, we should consider whether it is a good idea to include alogia (understood as the decrease in amount and spontaneous preparation of speech) in the negative dimension instead of in the cognitive one. The reason is that most of the mechanisms proposed to explain this sign are related to specific executive processes associated with the functioning of the frontal lobe. A recent study¹² on patients with schizophrenia found that alogia is associated with low performance on cognitive tests of planning, verbal fluency and concentration/attention.

The interest that negative symptoms have currently aroused in the scientific community is the result of social and clinical necessity. Negative symptoms are frequent in schizophrenia; almost 60% of patients in treatment present at least 1 negative symptom and 18% present the 3 negative symptoms assessed by PANSS (asociality, flattening of affect and alogia).¹³ In addition, between 15% and 30% of the individuals with schizophrenia present negative symptoms of such magnitude and persistence that the individuals are diagnosed as having deficit syndrome.^{6,14} These symptoms are already present at the beginning of the disease, even before the positive symptoms, and they lack appropriate assessment tools and effective treatments. Likewise, together with cognitive symptoms, they produce the greatest impact on functioning, life-style habits and somatic health of the individuals manifesting them. Numerous studies have shown a positive correlation between the seriousness of the negative symptoms and deterioration in the patient's social, family and work functioning; these studies also show that anticipatory anhedonia and avolition are the symptoms that seem to be the most relevant.^{9,13,15–17} That is to say, these symptoms would be largely responsible for the *early lack of functioning* that characterises schizophrenia. That is why it is so surprising that, although deterioration in social, family and work functioning is a required criterion for a diagnosis of schizophrenia, negative symptoms have so little weight for diagnosis in the universal diagnostic classifications (CIE and DSM).

Identifying and assessing negative syndrome is another of the areas that show insufficiencies. In day-to-day clinical practice, the recognition, assessment and recording of these negative symptoms are lower than that of positive ones (in part due to limitations of assessment tools), despite the persistence and impact on patient functioning of negative symptoms. However, thanks to NIMH initiative, psychometric assessment is undergoing extensive development and a methodological refinement to avoid the main problems presented by the instruments for assessing these clinical manifestations: validity of inappropriate conduct and use of behavioural referents instead of experiential ones. Under these premises, 2 new instruments have been developed, the Brief Negative Symptom Scale (BNSS)¹⁸ and the Clinical Assessment Interview For Negative Symptoms (CAINS).¹⁹ Both these tools show appropriate content validity—both incorporate the 5 negative symptoms identified and differentiate between anticipatory and experiential anhedonia—that focuses on assessment of the experiences lived by the patient in the 3 experiential negative symptoms (asociality, anhedonia and avolition) and observation of behaviour in the 2 expressive negative symptoms (flattening of affect and alogia).

Consequently, 2 generations of instruments can be considered at present, the 1st and 2nd. The first-generation instruments include the Scale For Assessment Of Negative Symptoms (SANS)²⁰ and the Positive And Negative Symptom Scale (PANSS)²¹ in schizophrenia. The second-generation instruments, both developed through NIMH initiative, are the BNSS¹⁸ and the CAINS.¹⁹ The Negative Symptom Assessment (NSA)²² scale represents the transition between both generations. Its content validity is suitable, as it includes the 5 negative symptoms. However, a behavioural focus is adopted in several of its items instead of the experiential, which would be more appropriate. Kane²³ recently gave an excellent review of the state of development of the instruments available.

In the psychometric area, the first-generation instruments have evolved and new versions have appeared: Levine and Leucht²⁴ developed a short version of SANS in 2012 and, in 1997, Marder et al²⁵ extracted a new negative subscale or factor of the PANSS using principal components analysis. In addition, the NSA has evolved towards shorter versions, such as the NSA-16 in 1993²⁶ and the NSA-4 in 2010.²⁷ However, although these new versions include important modifications, they still possess the limitations of the originals. Consequently, the future of assessment is probably in the hands of second-generation instruments.

An added challenge in understanding the negative syndrome lies in how difficult it is to develop clinical models (endophenotypes) based on new biomarkers and valid animal models that help us to identify its neurobiological substrate and to discover new therapy targets.²⁸ The negative dimension of schizophrenia is closely related to a series of complex functions that humans have been acquiring throughout our evolution and that distinguish us from the rest of all living things. Although you could argue that animal models can reproduce complex social behaviours, partly homologous to those of humans, they are still behavioural models that detect surface behavioural expression but not the internal experience the subject lives through and that defines the negative symptoms as we have just seen. To address this challenge, investigators in clinical research and animal behaviour and behavioural ecologists need to work together closely.²⁹

The lack of effective treatments for the negative dimension of schizophrenia reflects the difficulties in the other areas, concepts and limits, underlying pathophysiological mechanisms, and valid, reliable psychometric assessment. Initially, the second-generation antipsychotic drugs raised expectations about their effectiveness in negative symptoms; however, both studies and clinical practice have shown their lack of efficacy on primary negative symptoms in monotherapy and in multiple-drug therapy.³⁰ Researchers are focusing on new therapeutic options specific for negative symptoms, such as cannabidiol, oxytocin, alpha-7 nicotinic receptor antagonists, glycine transport inhibitors and metabotropic glutamate (mGlu) modulators. These studies are in varying phases of development and the results obtained until now have been promising in some cases. Undoubtedly, this will contribute to rescue this clinical area from the therapeutic nihilism and negligence that now characterises it.

References

1. Kirpatrick B, Fenton W, Carpenter WT, Marder ST. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr Bull.* 2006;32:296–303.
2. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biol Psychiatry.* 2004;56:301–7.
3. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull.* 2006;32:238–45.
4. Crow TJ. Positive and negative schizophrenic symptoms and the role of dopamine. *Br J Psychiatry.* 1980;137:383–6.
5. Berrios GE. Positive and negative symptoms and Jackson. *Arch Gen Psychiatry.* 1985;42:95–7.
6. Carpenter Jr WT, Heinrichs DW, Wagman AM. Deficit and non-deficit forms of schizophrenia: the concept. *Am J Psychiatry.* 1988;145:578–83.
7. Peralta V, Cuesta MJ, Martinez-Larrea A, Serrano JF. Differentiating primary from secondary negative symptoms in schizophrenia: a study of neuroleptic-naive patients before and after treatment. *Am J Psychiatry.* 2000;157:1461–6.
8. Horan WP. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophr Res.* 2011;132:140–5.
9. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinction between anticipatory and consummatory pleasure. *Schizophr Res.* 2007;93:253–60.
10. Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: a review of assessment strategies. *Schizophr Bull.* 2006;32:259–73.
11. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophr Bull.* 2006;32:250–8.
12. Berenbaum H, Kerns JG, Vernon LL, Gomez JJ. Cognitive correlates of schizophrenia signs and symptoms: I. Verbal communication disturbances. *Psychiatry Res.* 2008;159:147–56.
13. Bobes J, Arango C, Garcia-Garcia M, Rejas J, on behalf of the CLAMORS Study Collaborative Group. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS Study. *J Clin Psychiatry.* 2010;71:280–6.
14. Arango C, Kirkpatrick B, Buchanan RW, Carpenter WT. El síndrome deficitario: un dominio dentro de la esquizofrenia. *Actas Luso Esp Neurol Psiquiatr.* 1998;26:180–6.
15. Gard DE, Fisher M, Garrett C, Genevsky A, Vinogradov S. Motivation and its relationship to neurocognition, social cognition, and functional outcome in schizophrenia. *Schizophr Res.* 2009;115:74–81.
16. Foussias G, Remington G. Negative symptoms in schizophrenia: Avolition and Occam's razor. *Schizophr Bull.* 2010;36:359–69.
17. Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatr.* 2012;11:73–9.
18. Kirpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* 2011;37:300–5.
19. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. *Am J Psychiatry.* 2013;170:165–72.
20. Andreasen NC. *Modified Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa; 1984.
21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261–71.
22. Alphas LD, Summerfelt A, Lann H, Muller RJ. The negative symptom assessment: a new instrument to assess negative symptoms in schizophrenia. *Psychopharmacol Bull.* 1989;25:159–63.
23. Kane JM. Tools to assess negative symptoms in schizophrenia. *J Clin Psychiatry.* 2013;74:e12. <http://dx.doi.org/10.4088/JCP.12045tx2c>.
24. Levine SZ, Leucht S. Psychometric analysis in support of shortening the Scale for the Assessment of Negative Symptoms. *Eur Neuropsychopharmacol.* 2012. <http://dx.doi.org/10.1016/j.euroneuro.2012.11.008>.
25. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: Combined results of the North American trials. *J Clin Psychiatry.* 1997;58:538–46.
26. Axelrod BN, Goldman RS, Alphas LD. Validation of the 16-item negative symptom assessment. *J Psychiatr Res.* 1993;27:253–8.
27. Alphas L, Morlock R, Coon C, van Willigenburg A, Panagides J. The 4-item negative symptom assessment (NSA-4) instrument: A simple tool for evaluating negative symptoms in schizophrenia following brief training. *Psychiatry.* 2010;7:26–32.
28. Carpenter WT. It is time for a new paradigm for the study of psychoses. *Rev Psiquiatr Salud Ment (Barc).* 2010;3:1–3.
29. Shepard PD. Modeling negative symptoms: What's missing? *Schizophr Bull.* 2006;32:403–4.
30. Stahl SM. Emerging guidelines for the use of antipsychotic polypharmacy. *Rev Psiquiatr Salud Ment (Barc).* 2013;6:97–100.