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The Final thesis

**Evaluation of Negative Symptoms in Schizophrenia Using Standardized Assessment Tools.  
Literature Review**

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## **Summary**

This narrative literature review explores the most prominent standardized tools for the assessment of negative symptoms in schizophrenia in a chronological order. It begins by giving a short history of negative symptoms in schizophrenia and explains how they are viewed today. It then showcases the development of the tools to this day by their respective generations and explains their unique advantages and disadvantages, while considering their theoretical and practical virtues. The work also includes examples of the very recently developed digital methods, as it explores what new potentialities these methods can give us which have been hitherto unavailable. In the end, based on previous considerations given, the work gives answers as to why there is not simply one tool overshadowing all the others. Reasons are given why this is the case and why such a tool is not possible at the moment. Such a tool not being available at the moment need not imply that such a tool is impossible, and so the work briefly explores if such a tool could be possible in principle.

## **Keywords**

“Negative symptoms”, “Schizophrenia”, “Assessment tools”

## **Literature selection strategy**

Literature was taken from PubMed, Google Scholar, EuropePMC and VU Library on various dates beginning in 28.12.2022. The search words that were decided to be used were: “Negative symptoms schizophrenia”, “Assessment tools in schizophrenia”, “Standardized assessment tools in schizophrenia”.

After searching basic literature about articles which featured discussions about the various tools, the searches were narrowed down to search literature about single tools specifically. This introduced new search words corresponding with the names of the tools: “BPRS”, “BPRS-E”, “PANSS”, “SANS”, “CAINS”, “MAP-SR”, “SNS” etc.

Literature was also searched for additional information regarding deficit schizophrenia from google scholar, with the search words “deficit schizophrenia”.

Literature about the history of schizophrenia, especially regarding negative symptoms, was also searched on PubMed, Google Scholar, Europe PMC and VU Library. Various search

words were used: “History of schizophrenia”, “History of negative symptoms of schizophrenia”, “Negative symptoms in schizophrenia”.

The searches were not conducted in a systematic manner, various articles were included or omitted depending on if the article was deemed valuable in terms of the primary objective of this paper.

Articles which are not in English, articles which are about assessment tools which are not in English, articles which were not available, articles with redundant content, articles with no citations and articles with deficient referencing were not used in this paper. Articles which were published regarding the validation of a given assessment tool in a given language were also left out, as this narrative review is written on a more general level.

## **Introduction**

My goal is to present a narrative literature review about the currently standardized tools for the assessment of the negative symptoms of schizophrenia. In the latter part, I will also present some of the cutting-edge digital tools, which await more validation and standardization. First, I will shortly present when the concept of negative symptoms appeared, how thinking about it has developed, and where we are with regards to it today. Then, I will attempt to present the tools in a historically informed manner, where I will first discuss all the main tools which are hitherto available in a chronological order. In this section, I will also consider some of their advantages and disadvantages. The goal of this is to explicate why new and other tools were developed and are being developed: *Why is it that, today, there is not simply one tool that everyone would be satisfied with?* Moreover, could we have, *in principle*, one tool above all the others? In the end, I will conclude with what I consider to be the main reasons for why there is not simply one tool for the assessment of the negative symptoms of schizophrenia.

## **A brief history of schizophrenia – and its negativity**

The term *schizophrenia* itself was first coined by Eugen Bleuler in 1908 (1). His motivations for giving the name, was that he introduced a new understanding about what was formerly known as *Dementia Praecox*. *Dementia Praecox* was coined by the doctor Emil Kraepelin

already in 1878 (2). Dementia Praecox was a term that Kraepelin used to incorporate various descriptions of mental disorders of his time, known as *démence précoce*, juvenile insanity, catatonic syndrome, hebephrenia etc., what other scientists had described before him. What was common in all their descriptions, was that they typically affected the young and were often associated with chronic progression of the disease and disability (3). It is important to note that the classification was something which necessarily included various conditions within it, and not just one isolated disease. The term, Dementia Praecox, itself implies a dementia-like condition which occurs at a young age.

Eugen Bleuler was the first to notably criticize the term Dementia Praecox. He realized that Dementia Praecox was something which does not only occur in the young and that the disease is not static in the sense as the word dementia was understood to imply (1). Bleuler also saw use in being able to form nouns and adjectives with the new term: there is sense in calling a form of behavior schizophrenic but not “Dementia Praecoxic”. For Bleuler, schizophrenia was itself a grouping of various diseases within which all the conditions had something which he considered a breaking of mental abilities:

I call dementia praecox “schizophrenia” because (as I hope to demonstrate) the “splitting” of the different psychic functions is one of its most important characteristics. For the sake of convenience, I use the word in the singular although it is apparent that the group includes several diseases. (4 p.8)

This motivated his new term schizophrenia, which combines two Greek words, which together mean the splitting of the mind, soul, spirit or volition depending on how one wishes to translate *-phrēn* (φρήν). This idea has also carried onto other languages: In Finnish, schizophrenia could also be called “*jakomielitauti*” which implies a disease where the mind is split or divided.

The seeds for the development of the contemporary concept of negative symptoms in schizophrenia were already present at the time of Bleuler and Kraepelin. It is important to mention that Kraepelin did not consider negative symptoms to be something necessary in Dementia Praecox, while Bleuler emphasized the role of negative symptoms in basic forms of schizophrenia (5). Bleuler wrote about what he considered the fundamental symptoms of schizophrenia and one of them is what he calls disturbances of affectivity: “Many schizophrenics in the later stages cease to show any affect for years and even decades at a time. They sit about the institutions to which they are confined with expressionless faces,

hunched-up, the image of indifference.”(4 p.40). Such a symptom is what is today known as blunted affect, one of the agreed-upon negative symptoms of schizophrenia.

It’s important to note that what Bleuler called “negativism” can be quite different to the contemporary conception of negative symptoms:

We subsume under the term, negativism, a number of symptoms which have the common characteristic that a reaction which would be expected in a positive sense occurs in the negative sense instead. The patients cannot or will not do what is expected of them (passive negativism); or they do just the very opposite or, at least, something else than what is expected (active or contrary negativism). When the patients should be getting up, they want to stay in bed. When they are supposed to be in bed, they want to get up. (4 p.191)

What Bleuler called passive negativism could be an example of what today is called amotivation, but his active or contrary negativism has no corollary in the contemporary conception of negative symptoms.

Bleuler already had an idea of there being positive and negative symptoms of schizophrenia. However, the more contemporary way of dividing schizophrenia into negative symptoms and positive symptoms had to wait until the 1980’s to be explicated.

In the year 1980, T. Crow proposed a division of schizophrenia into two syndromes, each with their own neurophysiological mechanisms (6). Type 1 syndrome was proposed to have the positive symptoms, which were considered hallucinations, delusions and thought disorders. Type 2 syndrome was proposed to have the negative symptoms. For him, these were affective flattening, poverty of speech and loss of drive. He proposed two different pathological processes for the two syndromes, the former having an increase in the amount of dopamine receptors and the latter being due to the loss of brain cells and due to structural changes.

In 1982, Andreasen and Olsen decided to develop criteria for dividing the schizophrenia syndrome into what they called three different types: positive, negative and mixed (7). They say that the goal here, was to divide different forms of schizophrenia by their characteristic ways of appearance or symptoms. Andreasen and Olsen thought of them as follows: Positive type was the kind of schizophrenia which has prominent delusions, hallucinations, thought disorders and bizarre behavior. Negative type was the kind where there is affective flattening, alogia, avolition, anhedonia and attentional impairment. In a mixed type, the positive

symptoms and negative symptoms are both present in such a way that one cannot say that one is more prominent than another.

Not only is it typical today to think of schizophrenia as having negative and positive symptoms, our understanding of what each of these means has developed since the days of Bleuler and since the early 1980s. Noteworthy for our purposes are the developments in the conception of negative symptoms especially.

More conceptual development occurred in 1988 when a further category of schizophrenia called deficit schizophrenia was proposed by Carpenter et al. in the *American Journal of Psychiatry* (8). They wanted to propose a way in which we should use the term “deficit symptoms”. For them, we should call deficit symptoms those kinds of negative symptoms which stay present in a stable manner. These are the kinds of symptoms which are unrelated to medications currently in- or out of use, and which may occur with or without positive symptoms, being such that they are unrelated to the domain of positive symptoms in their occurrence (9). The authors also proposed a set of criteria for determining if deficit schizophrenia is present (8).

The status of deficit schizophrenia is currently under debate. The European Psychiatric Association released a systematic review in 2019, where they found 9 reviews which support the distinction into deficit and non-deficit schizophrenia (10). The systematic review even found evidence which suggests that deficit schizophrenia could be considered a separate species of disease as opposed to non-deficit forms. Moreover, a recent meta-analysis compared the brains of people fitting the criteria of deficit schizophrenia with people who fit the criteria for non-deficit schizophrenia, and a healthy control group of people (11). The meta-analysis found out that people with deficit schizophrenia have their volumes of grey and white matter reduced when compared to controls, while people with non-deficit schizophrenia have a reduction in the total volume of brain tissue and white matter when compared to controls. The meta-analysis was the first of its kind to investigate this according to the authors. More studies will be needed to study the neuroanatomical bases of deficit schizophrenia and non-deficit schizophrenia.

A major development in the understanding of negative symptoms after the early 1980s is the realization that negative symptoms should be divided into primary and secondary negative symptoms. The distinction is made by the proper recognition of the causes of the symptoms. Primary negative symptoms are caused by the essential disease processes of schizophrenia,

while secondary negative symptoms have something non-essential to schizophrenia as their cause, such as social isolation or side-effects from anti-psychotic medications (12). It is of important note that primary negative symptoms have no available treatments while secondary negative symptoms could be treated (13).

### **Making(s) of a consensus – negativity in schizophrenia today**

In the current day, there's some consensus about the existence of five different negative symptoms or domains in schizophrenia, which are also the symptoms which the European Psychiatric Association recognizes as the five "domains" of negative symptoms (10,13–15). The EPA takes its guidance from the NIMH-MATRICES consensus statement released in 2006.

The NIMH-MATRICES (The National Institute of Mental Health – Measurement and Treatment Research to Improve Cognition in Schizophrenia) consensus statement on negative symptoms is the result of a consensus conference which took place in Maryland, USA, from the 26<sup>th</sup> to the 27<sup>th</sup> of January 2005 (15). Their goal was to review the data of the time with regards to negative symptoms and their domains, so that proper measures for these domains could be chosen in the future. This is in relation to the second goal of the conference, which was to initiate a process for the development of new assessment tools for the negative symptoms of schizophrenia, as the development for treatments regarding them was severely lacking, even some calling it the problem that will not go away (16). One cannot develop proven treatments, if one cannot reliably measure their effects.

The NIMH-MATRICES consensus statement pronounced that we should consider there to be five distinct domains of negative symptoms in schizophrenia: Avolition, Anhedonia, Alogia, Blunted affect and Asociality (15). The researchers agreed that there are significant and important correlations between the domains, but that the domains could nonetheless be separate therapeutic targets with their own neurobiological mechanisms. Importantly, cognitive impairments were ruled out of the domain of negative symptoms. The statement does however explicitly mention that the statement should not represent a consensus that no other domains should be included in the future, nor does it give definitive definitions for the given domains.

The NIMH-MATRICES consensus statement recommended the development of an assessment tool which would operate on the basis of the five domains recognized (15). Such a tool was suggested to be such that it could be used both in in-patient and out-patient settings and that it would be sensitive to change. It was recommended that the five domains should be clearly defined in the instrument. The participants considered the SANS to be hitherto the most important assessment tool for negative symptoms, but it was agreed that it has the weakness of including items which were deemed not to be a part of the negative symptom construct as defined in the consensus statement.

Today, we can consider the NIMH-MATRICES consensus statement a seminal moment, because that is the moment which is now used to differentiate the various assessment tools into the first-generation tools and second-generation tools. The second-generation tools are those which were developed after, and in light of, the NIMH-MATRICES consensus statement and the first-generation tools are those which came before (17).

### **The tools of the first generation**

Here I will introduce some of the instruments for the assessment of negative symptoms of schizophrenia which were made before the NIMH-MATRICES consensus statement on negative symptoms. I will also shortly describe some of their advantages and disadvantages.

### **The brief psychiatric rating scale (BPRS)**

It was first published in 1962 by Overall and Gorham (18). The goal of the authors was to give clinicians a tool with which to assess the progression of symptoms in a patient with schizophrenia. The 1962 version consisted of descriptions of 16 major symptoms of psychosis. The clinician would then fill out on a 7-step scale the degree to which the patient exhibited a symptom, 1 meaning “not-present” and 7 meaning “extremely severe”. The authors of the scale considered the symptoms to be relatively discrete from each other. The scale was recommended for use in situations which required speed and efficiency. Clinicians who are experienced with the BPRS should take 2 to 3 minutes to administer the scale questions after the recommended 18-minute interview (19). The intention was that other



rating scales would be used when more time was available and when one wanted to be more detailed in their assessment (18). The authors of the BPRS also recommended it to be used by two clinicians who would do the interview together and then fill out the rating scale independently and then the two scores would be averaged for the final score.

The BPRS was released at a time before contemporary classes of negative symptoms, and so it does not have the specific end of assessing them. For our purposes though, the BPRS does contain an assessment of “Blunted affect” which directly corresponds to one of the five negative symptoms of schizophrenia recognized today (18). “Uncooperativeness” and “Emotional withdrawal” may or may not correspond with the domain of asociality as per the definitions given in the original BPRS for those two symptoms. It could be assumed that patients with asociality, as it is understood today, would score higher points in those two categories. It could also be assumed, that a patient with alogia could also score points in the category of “Motor retardation”, as this category includes changes in speech.

The scale was first expanded already in 1965 by 2 symptoms, totaling 18 major symptoms of psychosis to be assessed (20). The added symptoms of “Excitement” and “Disorientation” do not correspond with any negative domains of schizophrenia recognized today.

Building on previous research, a group of researchers released the expanded BPRS (BPRS-E) rating scale in 1986 (21). The scale has a total of 24-items. First were added symptoms (bizarre behavior, self-neglect and suicidality) which are typical of schizophrenia in the prodromal phase. Another three were also added to account for the symptoms of the manic phase of someone with schizoaffective disorder or bipolar disorder (21).

Later researchers since then wanted to improve the reliability of the BPRS by introducing behavioral anchors or specific trainings methods for the interviewers using the tool (22).

In 2016, a group of researchers proposed a 26-item version of the BPRS while also suggesting modifications for the BPRS-E (23). As an example, the researchers added the item of “impoverished thinking” to be able to better track negative formal thought disorder. Moreover, inappropriate affect was separated into a whole new item, separated from the bizarre behavior item.

Even today, the BPRS could work as a transdiagnostic assessment tool in routine clinical work (24). However, the BPRS, even with its extended forms, failed to properly account for

the negative symptoms as such, and so a new tool was needed. A tool which would have as one of its primary purposes the assessment of negative symptoms.

### **Scale for the assessment of negative symptoms (SANS)**

The scale for the assessment of negative symptoms (SANS) was first published in 1982 by Nancy Andreasen (25). It was the first instrument designed for specifically the evaluation of negative symptoms of schizophrenia, when prior tools to it had assessed negative symptoms only as a part of others. The SANS was made to consist of 5 scales which assess 5 different negative symptoms. The negative symptoms measured in SANS are alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attentional impairment (25).

In the development of SANS, Andreasen says to have made 6 basic assumptions with regards to theory (26). The first, is that there are no pathognomonic signs of schizophrenia and so a wide array of symptoms must be assessed. The second, is that greatest reliability is achieved by using “objective observational findings”. Andreasen uses the example of the assessment of affective blunting, stating that its existence and severity is best assessed by viewing the patient and their behavior as opposed to focusing in on their “internal psychological state”. The third assumption made by Andreasen, is that rating scales “must build on cross-sectional evaluation.” This means that the evaluation of a symptom should occur during a specified time-window, depending on what is being studied. The time-window could be long, like when trying to see if diagnostic criteria are fulfilled or not, or they can be short such as when studying the effects of a treatment method.

The fourth assumption made by Andreasen, was that the symptoms which are being assessed should be defined in such a way, that they can in principle be able to be mapped onto corresponding neural mechanisms (26). The fifth assumption made, was that rating scales should not favor simplicity over comprehensive coverage. Otherwise, one could miss if one specific negative symptom reacts to a given change, in a situation where too few items are used. The sixth assumption made, was that an ideal item is such that it is sensitive to change.

Andreasen was not only interested in the negative symptoms of schizophrenia but also made a scale for the assessment of positive symptoms of schizophrenia (SAPS), which was intended to be used as a complementary instrument for the SANS (27).

## **Positive and negative syndrome scale (PANSS)**

The positive and negative syndrome scale (PANSS) was first published in 1987 by Kay, Fiszbein and Opler in the *Schizophrenia Bulletin* (28). The authors state that PANSS was made on the basis of the prior assessment tools which were in use at the time: the 18-item BPRS and the Psychopathology rating schedule. The 18 items were taken from the BPRS and 12 from the PRS. This made the PANSS a scale of 30 items, with 7 points for the rating of each symptom. According to the authors the 7 points represent the severity of each symptom, where 1 indicates “absent” and 7 indicates “extreme”. The patient is assessed in comparison to the definitions given for each item, and the severity is then scored on the 7-point rating. The authors state that of the 30 parameters chosen, 7 were chosen for the positive symptoms and another 7 for the negative symptoms a priori. The remaining 16 were chosen to account for general psychopathology. The authors intended for the assessment to be able to be accomplished in 40 to 50 minutes and requiring minimal retraining for the clinician.

The authors wanted to create an assessment tool which would equally represent positive and negative symptoms (28). The authors found motivation for making this distinction based on the work of Crow whose research they cite to legitimize the distinction into positive and negative symptoms. They also cite the works of Andreasen and Olsen from 1982, who also theorized about the distinctions of the positive and negative dimensions of schizophrenia. With the development process of PANSS, we can see that research into schizophrenia played a significant role in the development of tools to assess it.

The negative symptoms assessed by the PANSS are blunted affect, emotional withdrawal, poor rapport, passive-apatetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (28). The PANSS evaluates these 7 symptoms, as opposed to the 5 domains we are dealing with today. Of the 7 negative symptoms assessed in PANSS, none really assess anhedonia.

An advantage of the scale is that it allows for the assessment of positive-negative symptoms to each other and in relation to general psychopathology.

A disadvantage of the scale is that it is not necessarily so easy to administer, even though the authors intended for it to require minimal training. In 2011, a systematic review found out

that up to 62% of authors appear to misuse the calculations of PANSS, potentially leading to erroneous results (29). The scale also is not up to date regarding our current understanding of the 5 domains of negative symptoms.

Some have even considered PANSS to be the gold standard tool when it comes to assessing the efficacy of anti-psychotics (30). Part of the reasons for this is the time and place when PANSS was developed. PANSS was developed during a time when psychiatry as a field was trying to develop new atypical antipsychotics after the success of Clozapine. Such measures needed the development of a tool which could be used to monitor such efforts and so PANSS became cemented in pharmacological development (31). As such, the scale has an incredibly important role when developing and investigating novel anti-psychotic medications.

However, today the EPA recommends that PANSS should be complemented with a second-generation assessment tool in clinical trials, due to a changed conception of negative symptoms (10).

### **Negative symptom assessment scale (NSA)**

The first version of the tool was made already in 1989 by Alphas et al. as a 26-item scale (19,32).

It was made into a 16-item tool in 1993 by Axelrod BN et al. (33). The authors behind the NSA-16 wanted to develop a tool which could be used to assess not only the presence of negative symptoms in schizophrenia, but also their severity and range. The tool functions by assessing five factors: communication, emotion/affect, social involvement, motivation and retardation (33). These are measured by 16 items, which are graded on a 7-point Likert scale, where 1 point signifies absence and 6 signifies severe presence of a given symptom. 9 signifies that a given symptom cannot be assessed, so that we have 7 in total. The NSA-16 is largely used in therapeutic trials (10). The NSA-16 was released as the only tool which has an item measuring the overall severity of negative symptoms (34). Depending on the source, it is said that the NSA-16 takes 15-30 minutes to fill out, making it non-ideal for clinical situations (10,19,35).

In 2011, a 4-item version of the NSA was validated by Alphas et al. (35). The authors found that the accuracy of the tool was comparable to that of NSA-16, and the purpose of the

shortened instrument was to allow for usage in busy clinical settings, while retaining the essence of NSA-16. Consequently, the NSA-4 takes 4 of the items of NSA-16: Restricted speech quantity (item 2), Emotion: reduced range (item 5), Reduced social drive (item 8), Reduced interests (item 13). The authors state that the purpose was to include one item of each of the domains assessed in NSA-16.

Some have considered the main limitation of NSA its high reliance on subject function or behavior to assess the experiential aspect of the symptoms (36). For example, reduced social drive is assessed by looking at how often and what kind of interactions a subject has. Also, this scale should be complemented by a second-generation tool according to EPA recommendations (10).

### **Schedule for the deficit syndrome (SDS)**

It was first published in 1989 by Kirkpatrick et al. This tool was primarily meant to distinguish those with deficit schizophrenia from those with non-deficit schizophrenia (37). This tool is considered the gold standard tool for differentiating between cases of deficit and non-deficit schizophrenia (10,38).

### **The tools of the second generation**

These are the tools which were released after the NIMH-MATRICES consensus statement and drawing inspiration from it. Another innovation that occurs as we shift into the 2<sup>nd</sup> generation tools is a kind of an inward turn, where self-report scales are more utilized. The primary second-generation tools are the BNSS, CAINS, MAP-SR and SNS (17).

### **Brief negative symptom scale (BNSS)**

The first assessment tool to be released after the NIMH-MATRICES consensus statement was the Brief negative symptom scale, abbreviated as BNSS (39). It was released in 2011 by Fitzpatrick et al., one of the important figures in the making of the consensus statement itself.

The BNSS is a 13-item instrument, which is designed to account for the 5 domains specified in the NIMH-MATRICES consensus statement (39).

The authors of the BNSS wanted to make an assessment scale which would include all the domains listed in the consensus statement, with a separate subscale score for each (39). They also wanted to be able to make a distinction between consummatory and anticipatory anhedonia. Consummatory anhedonia is the failure to enjoy what one is doing, a failure of the human capacity to “like”. Anticipatory anhedonia is the failure to properly assess an incoming reward, a failure to assess the enjoyability of what might be. In this case, there is a failure to “want” (40). Anhedonia has long been recognized as an important part of the symptomology of schizophrenia, but it was only fairly recently that it has been shown that patients with schizophrenia do feel enjoyment in-the-moment (38 p.130). Anticipatory anhedonia is more characteristic of schizophrenia, although the degree or presence of it has depended on the kind of stimulus provided in studies (42).

The authors made the scale firstly for use in treatment trials but was to also be such that it could find uses outside of them, such as in psychological studies (39). Importantly, the authors say that they wanted to assert a distinction between what they called “internal experience” and “behavior”, so that the two could be separately assessed.

The BNSS has 13 items, which are divided into 6 subscales (39). The BNSS is done in the form of a semi-structured interview, which should take about 15 minutes to complete, according to the authors. The items are rated on a 7-point scale, ranging from 0 to 6.

The 6 subscales of the BNSS are Anhedonia, Distress, Asociality, Avolition, Blunted affect and Alogia (39). Five of these are directly corresponding to the domains outlined in the NIMH-MATRICES consensus statement. The authors divided the anhedonia subscale into 3 items: Intensity of pleasure during activities, Frequency of pleasure during activities and Intensity of expected pleasure from future activities (39). The authors thought that this allows to distinguish between consummatory and anticipatory anhedonia. The Asociality subscale was divided into two items: Behavior and Internal experience. The Avolition subscale was divided into two items the same way. The Blunted affect subscale was divided into three items: Facial expression, Vocal expression and Expressive gestures. The Alogia subscale was divided into two items: Quantity of speech and Spontaneous elaboration.

The authors of the BNSS also included a “Distress” subscale, which has only one item. This quantifies the absence of distress, namely that of normal distress. This subscale seemed to

validly measure the absence of dysphoria (39). The authors intended for the distress subscale to aid in the problem of pseudospecificity, where there is an issue with distinguishing between the primary and secondary negative symptoms of schizophrenia. The distress item was intended by the authors to be one of the advantages of the BNSS, but one could consider it also as a disadvantage as it introduces an item which is not listed in the NIMH-MATRICES consensus statement.

### **Clinical assessment interview for negative symptoms (CAINS)**

The Clinical Assessment Interview for Negative Symptoms (CAINS) was first released in 2013 by Kring et al (43). The CAINS is another tool which was born out of the NIMH-MATRICES consensus statement, taking into consideration its conception of negative symptoms (asociality, avolition, anhedonia, blunted affect, and alogia) and its call for the development of novel tools. The CAINS also wanted to address the “conceptual and psychometric limitations” of the tools which had been hitherto released (43). Moreover, CAINS assesses not only the behaviors of a patient but also their reported experiences.

The authors state that the development of CAINS began such that it included various items for assessment, but after the first study of the development process CAINS was limited to 16 items. The CAINS as it was released and as we have it today, consists of 13 items. The CAINS consists of two scales, one which assesses expression by 4 items and another that assesses motivation/pleasure by nine items. The items in the scale are rated on a numerical scale of 0-4, where severity increases the value. The items are assessed regarding the past week of the patient before the assessment, except for anticipatory anhedonia, which covers the upcoming week after the assessment (43).

CAINS assesses expression by facial expression, vocal prosody, gestures and speech (43).

The assessment of motivation and pleasure is split into three parts: social, vocational and recreational. Social aspects are family relationships, friendships, past-week pleasure and expected pleasure. Vocational aspects are motivation and expected pleasure. Recreational aspects are motivation, past-week pleasure and expected pleasure (43).

The advantages of CAINS are that it takes into consideration both the phenomenological aspects of schizophrenia as well as recent studies regarding the neuroscience of motivation, pleasure and affect processing (44). CAINS, like the BNSS, makes a distinction between anticipatory and consummatory anhedonia in the assessment. There is evidence that these two phenomenologically distinct concepts are also distinct in their neurobiological correlates (45).

One of the disadvantages of CAINS is that it can take a rather long time to complete one assessment, as the instrument is rather long. This may prove to be too much of a limitation in certain clinical environments, as it can take up to half an hour to complete (10). Another possible disadvantage is its splitting of negative symptoms into two dimensions. Furthermore, some have argued that CAINS in fact implies the existence of three separable domains of negative symptoms, not two (46).

### **Motivation and Pleasure scale – Self report (MAP-SR)**

The Motivation and Pleasure scale – self report (MAP-SR) was first published in 2013 by Llerena et al (47). The MAP-SR takes inspiration from CAINS, as the authors had the goal of developing a similar scale but such that it is based on patient self-reports. At first, the authors had the goal of assessing the two domains which CAINS assesses, expression and motivation/anhedonia. However, the authors removed the expression items during the development process, as the measures for expression were determined to be of poor reliability and validity. This left us with the MAP-SR as we have it today, which assesses motivation/anhedonia domains of negative symptoms by patient self-reports - as the name of the assessment tool suggests.

The authors wanted the MAP-SR then to consist of 18 items for the assessment of motivation and pleasure of a patient (47). Six of these items would measure consummatory and anticipatory pleasure with regards to social, recreational and work domains. The authors state that another six items were for assessing the patients with regards to their feelings and motivations to be around their family, romantic partners and/or friends. Three of these items were however dropped during development because of a low item-total correlation. Then the final six items were for assessing motivation with regards to motivation and effort with regards to activities, such as school and hobbies. The patient gives points from 0 to 4, where



0 means a lack of identification with an item and 4 means the opposite. The MAP-SR was released consisting of a total of 15 items.

A clear advantage of the MAP-SR is that it allows to save some time in a clinical context, as doctors will not have to spend their own time filling out the scale.

A disadvantage of the MAP-SR is that it only assesses one domain of the negative symptoms of schizophrenia, the motivation/anhedonia domain.

### **Self-assessment of negative symptoms (SNS)**

The self-assessment of negative symptoms (SNS) was first validated in 2016 by Dollfus et al. (48). The goal of the authors in developing the scale was to make an assessment scale focusing on the subjective experiences of the patient. They wanted to make a scale which the patients could fill out on their own, making them participate more in the treatment process. The authors say that they wanted to conform the scale to the conception of negative symptoms given in the NIMH-MATRICES consensus statement, so that the scale would assess the five domains of negative symptoms (asociality, blunted affect, anhedonia, alogia & avolition). In short, the goal of the SNS is to be a self-assessment scale which covers the five domains of negative symptoms.

The development of the SNS followed certain principles (48). The authors wanted each of the five domains to have their own subscore and that each of the items would focus as much as possible on the internal experiences of the patient. The idea was that the account of the internal experience would be complementary in cases where the SNS is given together with a scale focused on observation of the patient. The authors also wanted the SNS to distinguish between consummatory and anticipatory anhedonia, like other second-generation assessment tools before it. The most novel of the development principles, at least according to the authors, was the decision that items are given verbatim from those with schizophrenia. The idea being, that this captures better the experiences of people with schizophrenia and helps them to identify with the items. The authors state that the items were taken during focus groups from patients with schizophrenia in France, involving a total of 28 patients. The authors considered a clinical environment to be the primary setting for the usage of this instrument, the primary end of the instrument to be a tool to guide practitioners in treatment.

The scale consists of 20 items which the patient fills (48). The patient is given the task of marking the response which they think best characterizes their feelings over the past week or 7 days. There are three possible scores to be marked: 2 for strongly agree, 1 for somewhat agree and 0 for strongly disagree. From this it follows that the minimum score is 0/40 points, and the maximum is 40/40 points, indicating severe negative symptoms. To assess the five domains of negative symptoms, each of the five domains is given 4 items which are scored. The authors reported that patients were able to complete the questionnaire in 5 minutes.

A definite advantage of the SNS is that it is a second-generation assessment tool which a patient can complete relatively fast. It also covers all the five domains of negative symptoms. Even though the tool is based on self-reports and lacks observation from a practitioner, the tool has high sensitivity and specificity (49). The tool is thus also good evidence that people with schizophrenia can give accurate accounts of their negative symptoms. The tool can also predict a decrease in the health-related quality of life in people with schizophrenia, especially its avolition subscore (50).

The authors of the tool reported “satisfactory acceptance” by the patients towards the tool (48). What exactly this means, is not explained in the original article of the tool’s validation. It could be assumed, that a possible disadvantage of the tool in people with schizophrenia is the possible unwillingness of patients to report their feelings to others. One could assume that a patient with paranoia and/or anosognosia would be less than co-operative with the assessment tool. This is of course a critique which can be landed against any assessment tool which requires some modicum of co-operation from the patient.

### **Assessment in a digital world – An incoming 3<sup>rd</sup> generation of assessment tools?**

In its wake, an increasingly digitalized world is bringing more possibilities for the assessment of negative symptoms in schizophrenia. In this section, I want to summarize and give examples of novel methods which digitalization has made possible.

A recent development in assessment tools is the usage of digital methods for the assessment of functioning. A recent narrative review gave good introductions of emerging assessment tools of functioning: active ecological momentary assessments (EMAs) and passive sensory-driven data collection (51).

EMAs capture the functional status of a patient in a given moment (52). With EMAs, the patients self-report their condition as their mobile device prompts them to. A possible advantage, when applied to the assessment of negative symptoms, is the countering of phenomena where patients fail to give proper judgements by retrospection about the symptoms and emotions they have had in the recent past.

The narrative review found various passive methods which are used to detect functional changes associated with the negative and cognitive symptoms of schizophrenia (51). These can be monitoring the movement of the subject away from home, their general physical activity as assessed by, for example, heart rate and step count. Moreover, sociability could be assessed by counting incoming and outgoing messages. Even applications have been developed for such purposes (53).

One such a passive method is the possibility of tracking patient's movements by the global positioning system (GPS). A recent case control study published in 2019 by Depp et al. studied GPS mobility as a digital biomarker of negative symptoms in schizophrenia (54). The GPS system which provided information was in the mobile phones of the patients. The study found that GPS mobility correlated well with EMAs which the study subjects would give, giving good evidence that GPS monitoring tracks the true movements of the subjects. The study also found that less GPS mobility was related to higher negative symptoms severity, especially diminished motivation. CAINS and SANS were involved in assessing the negative symptoms severity.

The authors note that GPS monitoring, and other such passive monitoring methods have some advantages over EMAs (54). One such an advantage is that it is less burdening on the patients, as they themselves do not have to give answers. Another one mentioned is that EMA studies generally gather information from a duration of one to two weeks while GPS monitoring does not have such a time limit.

A study by Cohen et al. in 2020 studied the phenotyping of blunted affect and alogia by mobile phone assessment (55). The goal of the study was to take first steps towards new assessment tools, as the treatments for negative symptoms and knowledge about their pathophysiology are still lacking. The authors state that the study was possibly the first of its kind, where video material is collected from patients with schizophrenia via mobile phones in an ambulatory setting and then analyzed for signs of symptoms. In the study, the patients would fill out EMAs and in the end, they would record a short video of themselves describing

their past hour. The videos were analyzed by computer programs, which would give a score based on the probability that a given emotion is being shown. Another computer program would analyze the acoustics of speech and quantify the physically measurable properties of speech i.e., frequency and volume. The data was shown to strongly converge with the results gathered from the patients by BNSS. The authors note that one of the advantages of such a method compared to traditional assessment tools, is that this method was shown in the study to better capture the dynamic changing and the ebb-and-flow nature of the negative symptoms. More traditional instruments only give snapshots of the everyday symptomatology of a given patient, while this is more sensitive to changes and so gives better “resolution”.

Another method which uses the mobile phones of patients are the measures of facial and vocal markers. An observational study published in 2022 by Abbas et al. demonstrated the use of a mobile phone application which gathered data about the facial and vocal markers of patients (56). The patients would complete assessments on their phones in which they had to describe images, make the most expressive face they can and give an answer to a simple question. This way, the researchers gathered data on the expressivity and free speech of patients, evoked facial expressions, and evoked vocal expressions. The data would then be processed by machine-learning algorithms which would detect vocal and facial markers. In the study, vocal markers were found to give strong signals for the severity of negative symptoms. Facial markers only gave signals for the severity of negative symptoms via prompted expressions. The study did suffer limitations which the authors acknowledged. The authors state that the sample sizes in the study were small and the negative symptoms were assessed using PANSS rather than a second-generation tool such as BNSS or CAINS. Nonetheless, the study gives more evidence in terms of its primary hypothesis, namely that facial and vocal markers could be used to assess the negative symptoms of schizophrenia.

It could be assumed that people with psychotic disorder would be less-than excited for tools which monitor their lives, especially if their disorder is associated with paranoia. One study, which specifically did not have monetary compensations for using EMAs, found out that acceptability amongst patients with schizophrenia spectrum disorders was relatively low with regards to EMAs when receiving no pay (57). The study found that higher acceptability rates were associated with young age and good premorbid adjustment.

One interesting and cutting-edge method for assessing negative symptoms is the usage of computational assessment to assess language. In 2022 a group of researchers in Rio de Janeiro published an article which was about how the connectedness of narratives and emotional words in them is related to the negative symptoms of psychosis (58). The researchers used an elicitation protocol, where the subjects of the study were told to come up with a narrative based on pictures given to them. The narratives would then be analyzed by computer software. The researchers discovered that connectedness of the narratives was correlated with negative symptoms, where the more severe the negative symptoms were, the connectedness of the narratives would decrease. Perhaps in the future, we will use computerized systems to help us analyze the narratives of patients, helping us form diagnoses and assess the severity of negative symptoms.

A very recent review article in the Schizophrenia Bulletin considers there to be three categories of tools used in remote assessment: Giving existing negative symptom scales remotely, direct inference of negative symptoms by patient activity, and EMAs (59). The methods discussed here can be fit into the latter two of these categories. The authors note that it was the COVID-19 pandemic which greatly boosted the development of these remote assessment tools (59).

The digital methods for the assessment of negative symptoms are a new and interesting method but because of its novelty more research into it is required. Moreover, because it is so new, so far, no standardization has occurred with regards to these methods which makes for another new and interesting field of study.

### **Discussion – One tool to rule them all?**

Ever since the first conception of schizophrenia, the concept of negative symptoms has accompanied it. Nonetheless, many decades had to pass before the first assessment tools which had the primary end of assessing negative symptoms. Today, there are various assessment tools which have this purpose, but why is there not just one above all the others? Could there be one?

One of the obstacles facing the development of such a tool today is the lack of knowledge about the pathophysiological mechanisms behind the negative symptoms of schizophrenia. A

big leap was made in the 1980s with regards to the development of tools when the works of Andreasen, Olsen and TJ Crow were used to categorize the symptomology of schizophrenia into the positive and negative domains of symptoms (6,7). A big leap was them being able to theorize the distinction not only on the basis of behavior but also on the basis of neurophysiological correlates behind such behavior. Since then, our conception of negative symptoms shifted with the NIMH-MATRICES consensus statement (15,17). It seems to me that the neurophysiological correlates of the negative symptom domains as defined in the consensus statement must be further defined and discovered for the development of an ultimate tool. Further knowledge into the biology of schizophrenia will be necessary so that one distinguish the domains of negative symptoms by their neurophysiology. This would help us to properly differentiate between not only primary and secondary negative symptoms but allow to further distinguish between various similar but different forms of negative symptoms such as between consummatory and anticipatory anhedonia. Being able to make accurate neurophysiological distinctions between the different negative symptoms of schizophrenia would be a giant leap forward in terms of also being able to give accurate definitions for the negative symptoms, which were not given in the NIMH-MATRICES consensus statement. The consensus which was reached is an important one, but without defining the terms which we claim to agree upon, the consensus risks ending up an illusory one. The defining and discovering of the neurophysiological mechanisms behind the symptoms are also important in terms of pharmacological research.

As described in the section about the theoretical origins of SANS, it was important for Andreasen that a symptom scale would use “objective observational findings” (26). A development against this idea occurs at the advent of the second-generation assessment tools. There occurs an inward turn as the tools start to ask after the experiential aspects which the patients report about how they are feeling, as opposed to their behaviors as such. The using of verbatim items in the SNS is one such an example. I claim that an ultimate tool would synthesize the two views, where the objective observational findings and patient self-reports would both be used in a manner where they are synthesized.

Another one of the obstacles towards the development of an ultimate tools for the assessment of negative symptoms is the status of deficit schizophrenia. As mentioned earlier, there is still an ongoing debate as to how we should understand its place in relation with schizophrenia as a whole (10). Is deficit schizophrenia a disease separate from non-deficits forms or something

else? This question needs answering before one can begin to think of how the schedule for deficit schizophrenia would be incorporated into a hypothetical ultimate assessment tool.

With the current assessment tools available, some are better for clinical contexts, some for assessing deficit schizophrenia and others such as the PANSS are preferred to be used in clinical trials for new medications. Many of the first generation assessment tools are recommended by EPA to be complemented today by other second-generation assessment tools for further accuracy in accordance with the NIMH-MATRICES consensus statement (10). Moreover, one needs the SDS to assess deficit schizophrenia and no other at the moment will do. If there was to be one, single assessment tool for negative symptoms of schizophrenia, it would have to be able to incorporate and surpass all of them at their respective goals.

As discussed earlier, Bleuler already saw schizophrenia as being a grouping of various diseases (4 p.8). Today researchers speak of the “endophenotypes” of schizophrenia, which are traits associated with schizophrenia but observable even in some of those without the illness and especially in unaffected family members of people with schizophrenia (60). It could be assumed, that the variance in the acquisition of these traits contributes to the heterogeneity of schizophrenia. The heterogeneity then makes for a necessity of various assessment tools.

As we proceed further into a digital age, the tools which it provides us give us certain advantages which were undiscovered at time of the NIMH-MATRICES consensus statement in the mid-00s. Assessment tools in the forms of questionnaires and interviews which the clinicians use give us snapshots of the negative symptoms which a patient experiences throughout their daily lives. Many of the digital tools such as EMAs can provide us with more information about how the negative symptoms change throughout these daily lives, which the pre-digital tools cannot. EMAs can give us better accounts of symptoms by self-reports but there are also digital methods which could give us more objective information. These could be such things as GPS-tracking of patient movements or natural language processing algorithms or even artificial intelligences. In some such a way, digitalization could provide us with tools with which to synthesize the contradiction between the first-generation focus on objective methods for assessment with the second-generation subjective methods for assessment.

## Results

The reasons for why there is not a single assessment tool are multiple:

- 1) Lack of knowledge regarding the pathophysiology of the negative symptoms of schizophrenia.
- 2) Unclear definitions for the agreed-upon negative symptoms of schizophrenia.
- 3) Lack of theoretical unity between the first- and second-generation tools leading to respective methodological differences.
- 4) Lack of knowledge about deficit schizophrenia leading to a lack of consensus regarding its status with regards to schizophrenia as a whole.
- 5) Some tools are better suited in other situations than others, which leads to a practical necessity to have many tools.
- 6) The inherent heterogeneity of schizophrenia creates a necessity for a multitude of assessment tools.
- 7) The question of how novel digital methods are to be incorporated in the assessment of negative symptoms. We know there are some advantages hitherto inaccessible, but we lack any standardization for these new methods.

For the reasons listed above, it seems to me that currently there is no possibility for the development of a single, or ultimate assessment tool for the negative symptoms of schizophrenia. With so many unanswered questions and lack of knowledge, any attempts at a grand unification are sure to fail.

This, however, does not mean that *in principle* there could not be one assessment tool for the assessment of negative symptoms of schizophrenia. On the contrary, if we were to overcome the reasons listed above, then I see no reasons as to why there could not be a single tool. The problem that I see with that, however, is that any overcoming of all of the reasons listed above may shift our understanding of schizophrenia itself. Dementia Praecox once became schizophrenia, and it could be that with such a great leap in knowledge about schizophrenia it could be that what we now call schizophrenia would become unrecognizable for us today.



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