The current conceptualization of negative symptoms in schizophrenia

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Negative symptoms have long been conceptualized as a core aspect of schizophrenia. They play a key role in the functional outcome of the disorder, and their management represents a significant unmet need. Improvements in definition, characterization, assessment instruments and experimental models are needed in order to foster research aimed at developing effective interventions. A consensus has recently been reached on the following aspects: a) five constructs should be considered as negative symptoms, i.e. blunted affect, alogia, anhedonia, asociality and avolition; b) for each construct, symptoms due to identifiable factors, such as medication effects, psychotic symptoms or depression, should be distinguished from those regarded as primary; c) the five constructs cluster in two factors, one including blunted affect and alogia and the other consisting of anhedonia, avolition and asociality. In this paper, for each construct, we report the current definition; highlight differences among the main assessment instruments; illustrate quantitative measures, if available, and their relationship with the evaluations based on rating scales; and describe correlates as well as experimental models. We conclude that: a) the assessment of the negative symptom dimension has recently improved, but even current expert consensus-based instruments diverge on several aspects; b) the use of objective measures might contribute to overcome uncertainties about the reliability of rating scales, but these measures require further investigation and validation; c) the boundaries with other illness components, in particular neurocognition and social cognition, are not well defined; and d) without further reducing the heterogeneity within the negative symptom dimension, attempts to develop successful interventions are likely to lead to great efforts paid back by small rewards.

Key words: Negative symptoms, schizophrenia, blunted affect, alogia, anhedonia, asociality, avolition, expression factor, experiential factor, assessment instruments, objective measures, treatment

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The first conceptualizations of negative symptoms of schizophrenia date back to the early 19th century, when J. Haslam described in young people a mental illness characterized by blunted sensitivity and affective indifference[1]. J. Hughlings Jackson[2] regarded negative symptoms as reductions in aspects of higher cognitive and emotional functioning, while considering positive symptoms as "release phenomena", episodic distortions or exaggerations in normal function. E. Kraepelin[3] described negative symptoms of dementia praecox as a "weakening of those emotional activities which permanently form the mainsprings of volition, emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor and of ability for independent action", and E. Bleuler regarded affective blunting and emotional withdrawal as "fundamental" to schizophrenia, while defining hallucinations, delusions and catatonia as aspects of acute exacerbations[4].

In spite of the considerable attention received in those years, negative symptoms have long been neglected in the diagnosis and treatment of schizophrenia. During the 1970s, a renewed interest in these symptoms was elicited by Strauss et al[5], who re-asserted the primary and chronic nature of negative symptoms, while considering positive symptoms as a non-specific transient reaction to stress or biological causes.

During the 1980s, a dichotomic approach to schizophrenia classification was proposed by T. Crow[6], who described two subtypes: type I, characterized by positive symptoms (hallucinations and delusions), favourable response to antipsychotic medications, good cognitive abilities and an increase in dopaminergic D2 receptors, and type II, marked by negative symptoms (blunted affect, poverty of speech and loss of drive), poor response to antipsychotics, cognitive impairment and neuroanatomic abnormalities. N. Andreasen[7] also described a positive, a negative and a mixed subtype of schizophrenia. This dichotomic approach, however, showed several limitations, including the lack of diagnostic stability over time[8,9], limited prognostic implications[10,11], and an inconsistency with factor analyses of the psychopathology of schizophrenia, which systematically yielded more than two factors[12,13].

Carpenter et al[14] introduced the concept of deficit schizophrenia to identify a relatively homogeneous subgroup of patients characterized by the presence of primary and persistent negative symptoms since first presentation, cognitive deficits, insidious onset, poor premorbid adjustment and poor overall outcome[15,16]. Subsequent research provided some support to the hypothesis that deficit schizophrenia is a separate disease entity rather than the worst end of a severity continuum in schizophrenia[15,17-21].

Notwithstanding the role of negative symptoms in its characterization and outcome, schizophrenia can be diagnosed in the absence of these symptoms, although the dimensional approach proposed by the DSM-5 will hopefully result in a greater focus on this key aspect of the disorder.

More recently, the accumulating evidence concerning the impact of negative symptoms on real-life functioning of people with schizophrenia[22-30], as well as the development of new molecules[31-33], stimulation treatments and psychological programs targeting these symptoms[34,35], have generated a renewed interest in negative symptom conceptualizations.

It has been increasingly acknowledged that instruments often used to assess negative symptoms include some aspects

not relevant to that concept[36-38]. For instance, the Scale for the Assessment of Negative Symptoms (SANS)[39] includes aspects such as inattentiveness, poverty of content of speech, increased latency of response, blocking, inappropriate affect, poor grooming and hygiene, which are not related to the negative dimension of schizophrenia. The negative subscale of the Positive and Negative Syndrome Scale (PANSS)[40] includes difficulty in abstract and stereotyped thinking, whose relationship with the negative dimension is highly questionable[41]. Factor 2 of the Brief Psychiatric Rating Scale (BPRS)[42], often used as a proxy measure for negative symptoms, includes emotional withdrawal (i.e., deficiency in relating to the interviewer and interview situation), which can be due to paranoid delusions or disorganization, and motor retardation (i.e., reduction in energy level), which might be due to depression or catatonia.

During the past decade, a broad consensus has been reached on the inclusion of five constructs in the negative symptom dimension: blunted affect, alogia, anhedonia, asociality and avolition[43-46]. Hereafter, we review for each construct the current definition; the differences among the main assessment instruments; the available quantitative measures and their relationship with the evaluations based on rating scales; as well as the correlates and the experimental models. The evidence that the five constructs are reflected by a two-factor structure is discussed, and future implications for research highlighted.

BLUNTED AFFECT

Blunted affect is a decrease in the observed expression of emotion, i.e. facial and vocal expression, and expressive gestures[47-49]. The term is nowadays preferred to and distinguished from flat affect, which represents the extreme end of the spectrum of blunting.

Blunted affect is included in commonly used negative symptom rating scales, such as the PANSS, the SANS, the Clinical Assessment Interview for Negative Symptoms (CAINS)[45,46], and the Brief Negative Symptom Scale (BNSS)[50]. Its evaluation is based on the observed spontaneous expression of emotion during the clinical interview, or emotion expressions in response to prompts provided by the interviewer, rather than on the subjective experience of decreased emotional range.

In the PANSS, the focus of the assessment is on facial expression and communicative gestures. In the SANS, more features are taken into account: facial expression, expressive gestures, eye contact, affective responsivity and vocal inflections. On the other hand, some of the features included in the SANS assessment of blunted affect do not appear in more recently developed instruments for the evaluation of negative symptoms: in particular, inappropriate affect is currently regarded as an aspect of disorganization, while decreased spontaneous movements are regarded as unspecific and more relevant to the assessment of depression. In both the CAINS and the BNSS, facial expression, vocal expression and expressive gestures are rated as features of blunted affect.

Facial expression has been measured using observational coding systems, such as the Facial Action Coding System and its emotion variant[51,52], the Facial Expression Coding System[53]. The majority of studies reported that both medicated and unmedicated patients with schizophrenia, compared to healthy controls, show a reduction in facial expressions for all emotions, involving both frequency and intensity, up to the total lack of changes throughout a conversation and in response to different stimuli aimed to elicit an emotional response[54]. A significant correlation with blunted affect has generally been reported[54].

Studies based on electromyography have provided objective measures of facial expressions. Most of them reported that, in response to emotional stimuli, individuals with schizophrenia have comparable or less zygomatic activity (typically associated with positive emotion) and comparable or greater corrugator activity (typically associated with negative emotion)[55-58]. The increased activity of the corrugators does not necessarily index a greater emotion expression in subjects with schizophrenia, as the activity of this muscle also reflects effort, concentration or puzzlement. In addition, even if individuals with schizophrenia were not impaired in these subtle microexpressions of emotions, their failure to show observable expressions clearly detectable by people they interact with would still have an impact on their social interactions. Healey et al[59] investigated how well the general public, i.e. not clinicians and research examiners, recognizes facial emotion expressions of persons with schizophrenia compared to expressions of healthy individuals, and found that facial expressions of persons with schizophrenia were more poorly recognized and more easily misidentified as neutral.

The majority of studies comparing vocal expression in individuals with schizophrenia vs. healthy subjects reported less accurate spontaneous and voluntary vocal emotion expressions in the former. The impairment involves all speech parameters, suggesting a global deficit of prosody[60].

Studies aimed to provide an objective assessment of vocal expression in individuals with schizophrenia used methods of computerized acoustic analysis of speech. These studies confirmed the deficit of vocal expression in schizophrenia subjects as compared to healthy individuals; however, the magnitude of the deficit suggested a lower degree of impairment with respect to symptom rating scales[61]. The reasons for this discrepancy are not entirely clear. Vocal expression is a complex and likely multidimensional construct, and research is needed to clarify which aspects of this construct are most pertinent to schizophrenia pathology.

Expressive gestures include those made with the hands, head (e.g., nodding), shoulders (shrugging), and trunk (e.g., leaning forward). In social interactions, they help to define who is talking to whom, who will speak next, the reciprocal level of understanding, interest and attention to the ongoing conversation. An overall reduction in patients' nonverbal behaviour, including head and body movement, eye gaze and gestures, has been reported by a number of studies observing

patient's behaviour during two-way interactions with a psychiatrist[62-64].

Blunted affect is observed among individuals with schizophrenia both on and off medication, thus excluding the possibility that the symptom is always caused by antipsychotic agents[65-67].

The possibility that decreased emotion expression is due to a reduction of subject's internal emotion experience is not supported by available evidence, especially for negative emotions[54,60]. Findings on positive emotions are more controversial, and will be discussed in the section on anhedonia.

The main hypothesis on the pathogenesis of blunted affect and its components (diminished facial and vocal expression and expressive gestures) include abnormalities in emotion identification and discrimination and, more in general, perception of nonverbal social cues (facial affect, prosody, and body gestures), or deficits in motor activity. As to the first hypothesis, deficits in perception of nonverbal social cues have been reported in several studies[68,69]. However, an association between deficit in nonverbal social cue perception and diminished emotion expression or negative symptoms has not been found consistently[70].

As to the alternative hypothesis, i.e. a deficit of motor expression[54,71], it is worth mentioning that patients with motor abnormalities are prone to impairments in nonverbal communication. Underlying mechanisms may vary (e.g., abnormalities of the basal ganglia or frontal lobe dysfunctions), and may differ for the various components included in the assessment of blunted affect. An abnormal functioning of the mirror neuron system has also recently been hypothesized[72]. This hypothesis might link the deficit of social perception to the motor abnormalities by assuming that a dysfunction in mirror mechanism of gesture behaviour may underlie the patients' difficulties in producing gesture following demonstration by the examiner (imitation) or on verbal command (pantomime). However, we cannot assume that mechanisms underlying imitation or pantomime also apply to spontaneous expressive behaviour.

ALOGIA

Alogia is defined as a reduction in the quantity of speech and in its spontaneous elaboration. It is rated in commonly used negative symptom rating scales, such as the PANSS, SANS, CAINS and BNSS. Its evaluation is based on subject's language production during the clinical interview. The clinician rates the tendency to answer questions shortly, if not in monosyllables, throughout the interview. In the current conceptualization, alogia does not refer to impoverished content of speech.

In the PANSS, the symptom is named "lack of spontaneity and flow of conversation" and described as a decrease in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive impairment. The relevant item evaluates both the amount of speech and the subject's attitude to avoid communication, while the latter is not regarded as relevant in other assessment instruments (actually, a reduction in the amount of speech aimed at avoiding communication may reflect psychotic features, e.g. persecutory delusions).

In the SANS, in addition to the reduction in quantity of speech (poverty of speech), alogia includes several items excluded in recently developed assessment instruments for negative symptoms, i.e. poverty of content of speech, blocking and increased latency of response. In fact, the poverty of speech content may be due to formal thought disorder (e.g., circumstantiality or derailment), anxiety or perseveration.

The BNSS provides separate items for quantity of speech and spontaneous elaboration (i.e., the amount of information given beyond what is strictly necessary in order to respond to the interviewer's questions, regardless of its relevance or importance), while the CAINS contains a single item for quantity of speech and does not assess spontaneous elaboration.

Cohen et al[73] conducted a meta-analysis of studies using an objective analysis of natural speech in patients with schizophrenia compared with non-psychiatric controls. They found that the reduction in speech production (reflecting alogia) had a large effect size ($d=-.80$; $k=13$), mainly driven by measures of pause behaviour as opposed to other aspects of speech, such as the number of words/utterances, that were reduced as well, but with a moderate effect size. Whether clinicians' judgment of alogia severity is mainly driven by the number and length of pauses deserves further investigation.

Several studies suggest an association between alogia and poor performance on verbal fluency tasks[74-77]. According to Fervaha et al[78], the relationship with verbal fluency is specific to alogia, i.e. not generalizable to other negative symptoms, suggesting that the two constructs tap into a common underlying mechanism. This mechanism could be a deficit of the ability to retrieve information from memory[79], since previous research showed that a deficit of controlled retrieval specifically affects the latency between words produced on category fluency tasks[80,81].

Controlled retrieval is likely to involve at least two components, i.e. the controlled activation of information in memory and the selection of specific information from the retrieved one[82]. The two aspects are associated with the activity of different brain regions: the left anterior ventrolateral prefrontal cortex and the left mid-ventrolateral prefrontal cortex, respectively. It might be of interest for future research on alogia in schizophrenia to disentangle the different cognitive components of controlled retrieval.

Cohen et al[61,63] have developed the cognitive resource limitation model, arguing that speech production in social situations places high demands on multiple cognitive processes. If cognitive resources are limited, patients will reduce their speech production. The association of alogia with cognitive deficits affecting controlled retrieval[79], semantic memory[84] and verbal fluency[75] would not contradict this hypothesis. The stronger negative correlations of general cognitive ability with alogia and blunted affect than with avolition/apathy and asociality[29,85] would also support the cognitive resource limitation model.

ANHEDONIA

Anhedonia, i.e. the diminished capacity to experience pleasant emotions, has traditionally been regarded as a core feature of both depression and schizophrenia[86]. However, this issue has turned out to be more complex than previously thought. In fact, although experiences of positive emotion during interview-based clinical assessments appeared to be reduced in people with schizophrenia, the use of emotion induction procedures under controlled laboratory conditions has shown that patients with schizophrenia do not differ from non-psychiatric controls in their subjective reactions to emotionally charged stimuli[54,87,88]. This discrepancy with previous findings of high rates of anhedonia in schizophrenia is attributed to limitations of self-report instruments, thought to be more cognitively demanding than laboratory based measures, often relying on complex cognitive processes, subject to systematic biases[89,90], or reflecting high rates of comorbid depression[91].

According to recent research, the anhedonia construct should be divided into at least two distinct aspects: a reduced experience of pleasure derived from ongoing enjoyable activities, also called consummatory anhedonia, which seems to be relatively intact in schizophrenia, and a reduced ability to anticipate future pleasure, also called anticipatory anhedonia, which seems to characterize people with schizophrenia[92-94]. However, some studies failed to confirm that anticipatory anhedonia is specific to schizophrenia, as it was found also in depressed patients[95]. Moreover, these aspects of the hedonic experience deficit in schizophrenia are more often regarded as part of the multifaceted construct of motivation, in which the ability to anticipate reward and pleasure is important to motivate behaviour aimed to achieve an expected, but not currently available, pleasant experience[96].

The assessment of anhedonia is not homogeneous across rating scales. This symptom is not included in the PANSS negative subscale. In the SANS, it is rated together with asociality, taking into account the subject's interest for recreational and sexual activities, as well as his/her ability to feel intimacy and closeness and to establish and maintain relationships with friends and peers; no distinction is made between consummatory and anticipatory anhedonia.

In the BNSS, anhedonia is rated by three separate items, measuring intensity and frequency of past (last week) pleasure, and intensity of future pleasure. Each item evaluates recreational, social, work/school, and physical pleasure. The frequency assessment does not require a precise count of activities over the past week, but rather a global consideration of behaviour relative to that person's demographic characteristics.

In the CAINS, anhedonia is rated by five items: two of them measure the frequency of past week recreational and social activities, while the other three measure the expected frequency of pleasurable work/school, social and recreational activities in the next week. No item for physical pleasure is included.

Strauss and Gold[97] found a low convergence between CAINS and BNSS items assessing anhedonia, and offered several possible explanations for the finding: a) the BNSS rates both intensity and frequency of past week pleasurable activities and only the expected intensity of future pleasurable activities, while the CAINS only considers the frequency; b) the BNSS evaluates four domains of pleasurable activity (work/school, recreational, physical, and social activities), whereas the CAINS evaluates two domains (social and recreational activities); c) the BNSS encourages the use of probe questions to help the subject to identify past and future pleasant activities, while the CAINS highlights the importance of avoiding probe questions relevant to expected pleasure, because the clinical goal is to assess the capacity to generate these expected events and activities.

In addition to rating scales, several self-assessment instruments, not developed and validated for schizophrenia specifically, are available for measuring anhedonia, such as the revised Social Anhedonia Scale (SAS)[98], evaluating pleasure in social activities; the revised Physical Anhedonia Scale (PAS)[99], measuring pleasure for physical stimuli; the Temporal Experience of Pleasure Scale (TEPS)[100], assessing trait anticipatory pleasure and consummatory pleasure; and the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)[101], that rates both consummatory and anticipatory social pleasure.

So far, few studies have explored correlations between self-assessed and observer-rated anhedonia. Overall, the measures appear to be poorly correlated[97,102,103]. Whether this is due to the different assessment modality or to the different facets of anhedonia explored by the various instruments should be addressed in future research.

Abnormalities of pleasure experience in schizophrenia have also been conceptualized as difficulties in reporting past or future experiences[54], and the proposal has been made to avoid the term "anhedonia" and replace it with "reduced pleasure-seeking behaviour" or "beliefs of low pleasure"[54,104]. Recent evidence from cognitive neuroscience seems to lend support to this conceptualization, as it shows that anticipating future events relies upon the same neural processes involved in episodic memory[105,106].

In summary, the prevailing view today is that people with schizophrenia have a preserved ability to experience consummatory pleasure, but show a deficit in the anticipation of pleasure and the ability to engage in pleasure-seeking behaviours. The mechanisms underlying these deficits may be relevant to some aspects of motivation (e.g., reward anticipation or effort valuation) or of cognitive functioning (impaired episodic memory interfering with subject's ability to recall previous pleasant experiences).

ASOCIALITY

Asociality often predates the onset of schizophrenia[107], and also occurs in schizoid personality disorder and autism[108,109]. Commonalities and differences in phenomenology and pathophysiology across these disorders are still to be elucidated.

In people with schizophrenia, asociality is currently defined as a reduction in social initiative due to decreased interest in forming close relationships with others. It should not be defined in purely behavioural terms (i.e., whether the subject has or not social interactions and close relationships), but mainly as a reduction in motivation for social contacts (i.e., whether the subject values and desires social interactions and close social bonds)[46,50].

A reduction in social activities and contacts can be secondary to factors such as delusions and hallucinations, which can deteriorate relationships and other social ties; suspiciousness or depressed mood, that may induce withdrawal from social life; or lack of opportunities to establish and maintain social relationships. This distinction might have important clinical and research implications: adequate information on identifiable and treatable underlying causes of secondary negative symptoms might translate into better care for people with schizophrenia, although more systematic research is needed in this respect[38,110].

In the assessment of asociality, both the SANS and the PANSS mostly rely on subject's behaviour. In the SANS, asociality is rated by two items included in the same subscale as anhedonia: ability to feel intimacy and closeness, and relationships with friends and peers. Also in the PANSS asociality is rated by two items: poor rapport (rating based on the observed interpersonal behaviour during the course of interview) and passive, apathetic social withdrawal (rating based on the reports about patient's social behaviour provided by primary care workers or by relatives).

The CAINS and BNSS ratings are based on both internal motivation (interest and desire for close relationships and friendships) and behavioural aspects (actual engagement in social activities). In the BNSS, asociality inner-experience and behaviour are rated by separate items. In the CAINS, asociality items (motivation for close family/spouse/partner relationships and motivation for close friendships and romantic relationships) are subsumed under motivation for social relationships. Correlations between BNSS and CAINS items are moderate to high[97].

In spite of the pivotal role that asociality plays in schizophrenia course and outcome, few studies have explored its pathophysiological mechanisms. Currently, asociality is mostly regarded as social amotivation[111-113], and factor analyses showing that it loads on the same factor as avolition lend support to this view[43,49,112].

Felice Reddy et al[114] investigated asociality in schizophrenia using Gray's model of behavioural approach (i.e., behavioural activation system, BAS, relying on a reward system sensitive to appetitive stimuli and termination of punishment) and behavioural avoidance (i.e., behavioural inhibition system, BIS, sensitive to aversive stimuli, activated by anxiety, novelty, and fear stimuli, and responsible for inhibiting behaviour), and classified subjects according to the presence of negative symptoms and different levels of BIS and BAS scores. Among subjects with elevated negative symptoms, the authors identified two subgroups with different approach/avoidance profiles leading to asociality: one characterized by avoidance tendencies (high inhibition/moderate activation) and another characterized by lack of approach motivation (low inhibition/low activation). The former subgroup was interested in relationships, but avoided them because they were viewed as aversive and anxiety provoking; the latter did not value close friendship and showed diminished interest in people and reduced drive to develop close interpersonal bonds. Only the latter subgroup would meet the current definition of asociality.

Research addressing the relationship between asociality and social cognition also deserves attention. Social cognition refers to mental activities underlying social interactions, including perceiving, interpreting and generating responses to the intentions, dispositions and behaviours of others[115]. It is impaired in people with schizophrenia and contributes to their poor functional outcome[116-119]. The relationship between asociality and social cognition is likely to be complex: lowered motivation to participate in social activities might result in poor development of social cognition[120], or poor social cognition may result in a failure to experience reward signals during social interactions and translate into anhedonia, poor motivation and asociality.

Unfortunately, studies have generally looked at the association between negative symptoms in general (not focusing on asociality) and social cognition. Findings have been mixed, with some authors describing significant associations[121-124] and others reporting no association[125-127]. The reasons for these discrepancies may include the lack of focus on asociality as currently conceptualized and measured, but also the failure to control for confounding variables such as intellectual deficits, duration of illness or the use of assessment instruments for negative symptoms including cognitive measures or disorganization symptoms. Piskulic and Addington[128], for instance, reported that the PANSS negative scale item that emerged as the main predictor of social cognition variance was stereotyped thinking, i.e. an item that current conceptualizations would not place among negative symptoms. Thus, although a link between asociality and social cognition cannot be excluded, the extent and nature of this association is still to be clarified[129,130].

A relationship between dysfunctional beliefs and asociality has also been envisaged: negative expectancies about future rewards or success in social interactions would lead to a loss of motivation to engage in social activities[131].

Recently, several studies have suggested an involvement of oxytocin in asociality of patients with schizophrenia, as well as of people with autism spectrum disorders. In mammalian vertebrates, oxytocin is implicated in the central neuromodulation of social behaviour, and current research is trying to clarify its role in fine-tuning neuronal circuits underlying social interaction. An association between lower endogenous oxytocin levels and greater severity of negative symptoms, including asociality, has been found[132-134]. The relevance of these findings to the current conceptualization of asociality and their possible implications for treatment require further investigation.

AVOLITION

In the past decade, there has been a renewed interest in avolition, also due to the evidence that this symptom leads to severe impairments in real-life functioning[29,135] and predicts poor functional outcome[136,137] in people with schizophrenia.

Avolition is currently defined as reduced initiation and persistence of goal-directed activity. There is no agreement on the degree of overlap between the terms avolition, decreased drive, amotivation and apathy, and they are often considered interchangeable[138]. It is also highly debated whether the definition and assessment of avolition should rely upon the rater's or caregiver's observation of patient's behaviour, or patient's self-report of her/his engagement in different activities or self-declared interest in engaging in activities.

As for asociality, it is recommended not to base the ratings of avolition only on the observed behaviour. In fact, a failure to initiate and persist in goal-directed activities may be due to several factors that do not reflect negative symptoms (e.g., paranoid beliefs, depression or lack of opportunities). The assessment should always include the subject's desire and interest for goal-directed activities.

Clinical rating scales of avolition involve a retrospective assessment that often combines more than one source of information, whose correspondence has rarely been tested[139]. In the SANS, apathy/avolition is assessed by three items, all focusing on subject's behaviour: grooming and hygiene, impersistence at work/school, and physical anergia. In the PANSS, only one item actually refers to avolition, i.e. emotional withdrawal, which relies upon caregiver's report on patient's interest and emotional involvement in daily life. The BNSS includes separate items for avolition internal experience and avolition behaviour; both items cover motivation for work/school, recreational activity, self-care, and general time spent in inactivity. In the CAINS, avolition is assessed by two items of the scale "motivation and pleasure": motivation for work and school activities, and motivation for recreational activities. Inner experience and behaviour are rated within each single item; self-care is not rated. Correlations between BNSS and CAINS items are moderate to high, but lower than those observed for blunted affect and alogia[97].

According to current conceptualizations, motivation is a multifaceted construct, including hedonic experience, reward prediction and other elements, such as reward valuation, effort valuation, encoding of action-outcome contingency, and decision making processes[94]. This multifaceted framework closely resembles the conceptualization of motivation in the positive valence system within the Research Domain Criteria (RDoC) project[140], and in the last decade has become the object of several experimental models, that will be briefly reviewed hereafter.

The hypothesis that an impairment in reward functions undermines motivational aspects of the schizophrenia negative dimension has received great attention. It has been clarified that many subjects with schizophrenia experience pleasure as much as healthy subjects when engaging in pleasant activities during everyday life or when exposed to pleasant stimuli[92,141]; however, they less frequently engage in behaviours aimed at obtaining rewards and pleasurable outcomes[142], due to their failure to anticipate future rewards. Studies on reward anticipation in schizophrenia have mainly focused on the neurobiological underpinnings of this process, and consistently reported an impairment in reward prediction mechanisms mediated by striatal nuclei[93,143,144].

The ability to predict a reward requires a learning process. Therefore, several studies focused on reward learning processes in schizophrenia, and reported difficulties when rapid learning of reward cues is requested and changes in outcomes and feedbacks occur (e.g., a previously rewarded response is followed by punishment), while no differences are observed when subjects learn over many trials (habitual/procedural learning)[94,145,146].

The possibility has also been considered that the motivational deficit involves the ability to "represent value information", i.e. to link the hedonic properties of a stimulus with individual's internal state (e.g., food is more valuable to a hungry person), with the delay between the stimulus and the reward, as well as with the need to modify response contingencies (a previously rewarded stimulus that becomes associated with punishment). There is evidence that the ventromedial prefrontal cortex is involved in the representation of goal values[147].

Another approach to understanding the relationship between reward anticipation and avolition evaluates the amount of effort an individual is willing to exert for a certain amount of reward. Recent attention has focused on experimental paradigms that measure cognitive, perceptual and physical effort. Initial results from studies exploring the psychometric characteristics of different measures[148] appear promising. Tasks require an incrementally greater effort, either cognitive or physical, to obtain a monetary reward; the level of effort is increased from trial to trial to find the subject's "breakpoint", i.e. the point at which the subject is no longer willing to put effort to obtain the offered reward. Subjects with schizophrenia tend to have breakpoint scores lower than or equivalent to controls, and a lower breakpoint is significantly associated with greater severity of motivational deficit[149-154]. The brain areas that appear to be involved in computing the expected effort cost are the dorsomedial prefrontal cortex and the insular cortex[155].

The hypothesis that a deficit of executive functions contributes to subject's difficulty in engaging in goal-directed activity has also been supported by some research findings[156-158]. However, inconsistent results have been reported[46,85], and a more systematic assessment of both domains will help to identify reasons for discrepancies.

Notwithstanding the interest and progress brought about by the described experimental models, it is clear that the interaction of neural systems involved in motivation is a complex one, and we are probably just beginning to unravel this complexity. Besides the neural level, also the psychopathological level needs further refinement; in particular, the assessment should involve different instruments and sources of information,

and possible discrepancies should be highlighted. In addition, the possibility that personalizing reward (e.g., making monetary reward proportional to subject's income) could have an impact on patient-control differences should be addressed, and sources of secondary avolition carefully considered and possibly excluded.

FACTORS WITHIN NEGATIVE SYMPTOMS

Factor analyses of negative symptoms have demonstrated that the structure of these symptoms is not unidimensional. In studies focusing on the SANS, a number of factors ranging from two to five has emerged. However, the most replicated and stable structure (especially after excluding items unrelated to negative symptoms, such as inattentiveness or inappropriate affect) includes two factors, i.e. diminished expression and avolition[37,159,160]. Factor analyses on the Schedule for the Deficit Syndrome (SDS)[161], including six negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive), have confirmed the two factor structure[28,162,163]. The same model has been confirmed by factor analyses of most recent assessment instruments, the CAINS and the BNSS[46,50,164]. In the relevant literature, the two factors are often referred to by different terms: diminished expression is also named as the expression factor, and avolition as apathy or motivation and pleasure or the experiential factor[165].

For the BNSS, six items (facial expression, expressive gestures, vocal expression, spontaneous elaboration, quantity of speech, and lack of normal distress) load on the expressive factor, and seven (intensity of expected pleasure from future activities, asociality behaviour, asociality inner experience, avolition behaviour, avolition inner experience, intensity of pleasure during activities, and frequency of pleasure during activities) load on the avolition/apathy factor. The factor structure seems to be independent of medication[37,160,162,166] and to hold up across time[28] and cross-culturally[28,162,163,167].

Few studies have attempted to identify external validators of the two negative symptom subdomains. The avolition factor seems to be associated with poorer premorbid social adjustment in childhood, more insidious onset of psychosis, executive functioning and abstraction-flexibility deficits, and a preponderance of male gender[70,157], while the diminished expression factor with an abrupt onset of psychosis, longer duration of hospitalization and impaired overall cognitive performance[70,85]. However, discrepant findings have also been reported, in particular concerning relationships with cognitive functioning[29,158].

Recent research has shown that the two factors have a different impact on psychosocial outcome. In fact, a strong relationship between avolition and poor social outcome has been consistently found[137,157,168], whereas findings relevant to the expressive subdomain have been mixed, and generally negative when the role of avolition is simultaneously accounted for[29,137,168]. The possibility that the strong impact of avolition on real-life functioning is due to the partial overlap between these two constructs cannot be ruled out. However, findings from studies using instruments developed to assess negative symptoms based on inner experience (e.g., lack of interest and motivation in different activities, impaired anticipation of rewarding outcome), instead of behavioural aspects (e.g., deficit in initiating and persisting in different activities, which are generally the focus of real-life functioning assessment), would argue against this possibility[24,29,169].

In summary, the two-factor structure appears highly replicable across instruments, medication status and phase of the illness. It is advisable that future research on negative symptoms avoids combining the two subdomains in order not to lose information relevant to pathophysiological mechanisms and to the ability of each factor to predict functional outcome.

CONCLUSIONS

From time to time, the conceptualization of negative symptoms has changed. Sometimes they have been considered as a key feature of schizophrenia, at other times neglected because they are difficult to be reliably assessed. Currently, negative symptoms are regarded as a core aspect of schizophrenia with a pivotal role in its functional outcome. However, the pathophysiology of primary and persistent negative symptoms is still unknown and they remain a major challenge in the treatment of those suffering from the disorder.

The assessment of the negative symptom dimension has certainly improved. A large body of research has clarified that some symptoms previously included in the negative symptom dimension – such as inattentiveness, poverty of content of speech, increased latency of response, blocking, inappropriate affect, poor grooming and hygiene – are not negative symptoms. The constructs currently considered as relevant to the negative dimension include blunted affect, alogia, anhedonia, asociality and avolition. This reconceptualization has, among the others, the advantage of reducing the overlap of negative symptoms with the cognitive, disorganization and depression dimensions of schizophrenia.

Whether this will represent an enduring consensus is hard to predict. In fact, while the need to exclude constructs unrelated to negative symptoms is undisputable, the choice and definition of current constructs should be regarded as work in progress.

As highlighted for each construct, largely used assessment instruments vary in terms of definitions and assessment modalities. The evaluation of alogia and blunted affect provided by the SANS and the PANSS, for instance, is based on different items, some of which are no longer regarded as relevant to the negative symptom domain (e.g., poverty of content of speech, inappropriate affect). The assessment of anhedonia, avolition and asociality also varies greatly: anhedonia is not rated in the PANSS; it is rated together with asociality in the

SANS; it is subdivided into consummatory and anticipatory in the BNSS and CAINS, but not in the SANS. In addition, the assessment includes physical anhedonia in some instruments but not in others, and some scales focus on behaviour, while others privilege subject's internal experience.

In addition to differences across instruments, methodological differences within the same instrument might also have important implications in terms of reliability of the observed findings. In fact, while the evaluation of some constructs (alogia and blunted affect) is mostly based on rater's observation during the interview, for other domains (anhedonia, avolition and asociality) the assessment relies upon subject's or other informant's recollection of the recent past.

The BNSS and the CAINS are considered by most experts in the field as state of the art for the assessment of the negative dimension constructs. They have been translated in several languages and are used in several clinical trials. Multinational, multicenter trials, aimed at adapting these instruments to different cultural contexts and validating them across illness stages and medication status, represent a possible step forward in the standardization of the assessment of negative symptoms. Hopefully this will translate in more consistent and clinically relevant research findings.

In the scientific community, there is also a rising interest for self-rated instruments that do not require a significant investment of time and effort by clinicians and are likely to reflect patient's internal experience. However, the reliability of these measures and the consistency with examiner-rated assessment instruments is still uncertain.

Future studies aimed at clarifying the neurobiological substrates of negative symptoms or investigating new compounds as potential treatments might benefit from experimental designs that take into account: a) the need to distinguish negative symptoms due to identifiable causes (e.g., extrapyramidal symptoms, depression or positive symptoms) from the primary ones, and b) the need to assess individual negative symptoms. It should be stressed that, for the time being, there is no evidence behind the assumption that a common pathophysiological mechanism underlies all negative symptom constructs; therefore the use of a total score for the negative dimension, although attractive from a statistical point of view (having more than one endpoint to deal with requires appropriate statistics and sample sizes), might prevent important conclusions relevant to individual constructs.

The search for objective measures represents a commendable effort. Their use might overcome the dismissive attitudes toward negative symptoms, justified by uncertainties concerning the reliability of rating scales. However, the discrepancy with data provided by rating scales deserves attention, since it has generated new hypotheses and insight in the complexity of the constructs, but in some cases might also lead to potentially misleading conclusions. For instance, quantitative measures of the activity of facial muscles involved in emotional expression might show no difference between patients with schizophrenia and healthy subjects, but the failure of these patients to show observable expressions clearly detectable by people they interact with would still have an impact on their social interactions.

The exclusion of some aspects which were previously part of the assessment of negative symptoms has contributed to reduce their overlap with other illness dimensions. However, the boundaries and relationships with neurocognition and social cognition are not yet well defined. Alogia, for instance, like poor verbal fluency, has been conceptualized as a deficit in the ability to retrieve information from memory; a similar deficit might underlie difficulties in gesture and facial expressions; anhedonia as difficulty in reporting past or future experiences might rely on the same neural processes underlying deficits in episodic memory; and asociality might be the origin as well as the result of poor social cognition. Further studies, either based on longitudinal designs or network models, might contribute to clarify these issues.

Heterogeneity among, and even within, the different negative dimension constructs cannot always be addressed by considering all of them as study outcome measures. The two-factor structure, highly replicable across instruments, medication status and phase of the illness, has been proposed as an alternative to either the use of a total score or of five different scores. However, the assumption that domains within the same factor share the same neurobiological mechanisms and that these mechanisms differ between the two factors has still to be substantiated by empirical data. So far, we cannot rule out the possibility that different constructs load on the same factor because of reasons different from shared underlying neurobiology, such as the focus on the behavioural aspects during the interview for blunted affect and alogia, versus the more introspective and retrospective approach for the anhedonia/avolition/asociality factor.

For the time being, both lumping and splitting approaches should be pursued, especially in studies investigating pathophysiological mechanisms of negative symptoms. The identification of different neural processes underlying different symptoms/constructs might imply the need for therapeutic interventions with different mechanisms of action. Without reducing the heterogeneity within the negative symptom dimension, attempts to identify successful treatments are likely to lead to great efforts paid back by small rewards.

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