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Primary and persistent negative symptoms: Concepts, assessments and neurobiological bases

Armida Mucci [a,*], Eleonora Merlotti [a], Alp Üçok [b], André Aleman [c], Silvana Galderisi [a]

[a] Department of Psychiatry, University of Naples SUN, Naples, Italy
[b] Department of Psychiatry, Psychotic Disorders Research Program, Istanbul Faculty of Medicine, Istanbul, Turkey
[c] University of Groningen, University Medical Center Groningen, Department of Neuroscience and Department of Psychology, Groningen, The Netherlands

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ABSTRACT

Primary and persistent negative symptoms (PPNS) represent an unmet need in the care of people with schizophrenia. They have an unfavourable impact on real-life functioning and do not respond to available treatments. Underlying etiopathogenetic mechanisms of PPNS are still unknown. The presence of primary and enduring negative symptoms characterizes deficit schizophrenia (DS), proposed as a separate disease entity with respect to non-deficit schizophrenia (NDS). More recently, to reduce the heterogeneity of negative symptoms by using criteria easily applicable in the context of clinical trials, the concept of persistent negative symptoms (PNS) was developed.

Both PNS and DS constructs include enduring negative symptoms (at least 6months for PNS and 12months for DS) that do not respond to available treatments. PNS exclude secondary negative symptoms based on a cross-sectional evaluation of severity thresholds on commonly used rating scales for positive symptoms, depression and extrapyramidal side effects; the DS diagnosis, instead, excludes all potential sources of secondary negative symptoms based on a clinical longitudinal assessment.

In this paper we review the evolution of concepts and assessment modalities relevant to PPNS, data on prevalence of DS and PNS, as well as studies on clinical, neuropsychological, brain imaging electrophysiological and psychosocial functioning aspects of DS and PNS.

1. Primary and persistent negative symptoms: evolution of concepts and assessment

Negative symptoms of schizophrenia represent a heterogeneous clinical construct and different strategies have been proposed to reduce their heterogeneity in the context of clinical trials and neurobiological research. The distinction between primary negative symptoms, a core aspect of the illness (Carpenter et al., 1988) and negative symptoms secondary to other factors (e.g. positive symptoms, extrapyramidal side effects, depression or isolation) bears important therapeutic implications. In fact, while secondary negative symptoms can be improved by removing underlying identifiable causes, primary negative symptoms are likely to persist in spite of treatment with either conventional or second generation antipsychotics.

In 1988, Carpenter et al. introduced the concept of deficit schizophrenia (DS) to identify patients with schizophrenia showing primary and enduring negative symptoms. In 2001 Kirkpatrick et al. proposed that DS represent a separate disease entity with respect to non-deficit schizophrenia (NDS). Although the DS/NDS categorization can be made reliably, the information about the longitudinal course of the symptoms required to make the primary/secondary distinction may not always be available (Buchanan, 2007; Mäkinen et al., 2008). Moreover, the diagnosis of DS may be difficult in first-episode schizophrenia subjects.

A different approach aimed to reduce heterogeneity of negative symptoms was proposed within the frame of the National Institute of Mental Health initiative Consensus Development Conference on Negative Symptoms that led to a consensus on the definition of persistent negative symptoms (PNS) (Kirkpatrick et al., 2006; Buchanan, 2007)). Proposed criteria are easily applicable in the context of clinical trials: negative symptoms of at least moderate severity for an extended period of time (usually 6months), in the presence of low levels of positive, depressive and extrapyramidal symptoms, as assessed by cross-sectional evaluation of severity thresholds on commonly used rating scales (Buchanan, 2007). The present review will describe the evolution of concepts and assessment modalities relevant to PPNS and will

* Corresponding author at: Department of Psychiatry, Second University of Naples (SUN), L.go Madonna delle Grazie, 1, 80138 Naples, Italy.
E-mail address: armida.mucci@gmail.com (A. Mucci).

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summarize data on the prevalence of DS and PNS, as well as studies on clinical, neuropsychological, brain imaging electrophysiological and psychosocial functioning aspects of DS and PNS.

2. Deficit schizophrenia

2.1. Definition

DS is defined by the diagnostic criteria outlined in the Box 1. The categorization of patients into DS and NDS by means of the Schedule for the Deficit Syndrome (SDS, Kirkpatrick et al., 1989) has been shown to have good inter-rater reliability (Kirkpatrick et al., 1989; Fenton and McGlashan, 1994; Amador et al., 1999; Galderisi et al., 2002; Peralta and Cuesta, 2004) and a high degree of stability with good test-retest reliability (Kirkpatrick et al., 1993; Fenton and McGlashan, 1994; Amador et al., 1999; Tek et al., 2001; Galderisi et al., 2013a; Strauss et al., 2010; Peralta et al., 2014). The lowest percentage of stability was reported by Strauss et al. (2010) in a 20-year follow-up study (67% vs over 82% in Amador et al., 1999 and Galderisi et al., 2013a). It is not clear whether the method used to classify DS (a proxy method for Strauss et al and the SDS in the other 2 studies) or the length of the follow-up (20years in Strauss et al vs less than or equal to 5years in the other studies) might explain the difference in the percentage of stability.

After DS was first described, several studies comparing patients with DS to those with NDS provided data supporting the hypothesis that DS differs from NDS for risk factors, premorbid functioning, disease course, neurobiological correlates and response to treatment (Kirkpatrick et al., 2001, Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009; Cohen et al., 2010; Strauss et al., 2010; Galderisi et al., 2013a; Kirkpatrick, 2014).

Findings from investigations using taxometric statistical analyses (Blanchard et al., 2005; Ahmed et al., 2015) support the hypothesis that DS represents a separate disease entity with respect to NDS.

2.2. Assessment

The gold standard for the diagnosis of DS is the "Schedule for the Deficit Syndrome" (SDS, Kirkpatrick et al., 1989). The SDS is a semi-structured interview that can be carried out by psychiatrists, psychologists or social workers with clinical experience in schizophrenia. Its use requires an ad hoc training, in a session led by an expert of the use of the instrument. The SDS semistructured interview is conducted with the patient; the use of all other available sources of information, such as clinicians and family members, is strongly recommended to complete the schedule. The DS/NDS classification should be carried out during periods of clinical stability.

Box 1
Diagnostic criteria for the deficit syndrome (Carpenter et al., 1988; Kirkpatrick et al., 1989, 2001).

a) Presence of at least two out of the following six negative symptoms:

i. restricted affect (referring to observed behavior)
ii. diminished emotional range (i.e., reduced range of the patient's subjective emotional experience)
iii. poverty of speech
iv. curbing of interests
v. diminished sense of purpose
vi. diminished social drive;

b)presence of the above symptoms for at least 12 months including periods of clinical stability;c)the above symptoms are primary, i.e., not secondary to factors such as anxiety, drug effect, psychotic symptoms, intellectual disability or depression;d)the patient meets DSM (3rd edition or later editions) criteria for schizophrenia.

To increase the practicability of the DS diagnosis, Kirkpatrick et al. (1993) proposed the use of a proxy method (Proxy for the Deficit Syndrome, PDS). The first PDS was based on the Brief Psychiatric Rating Scale (BPRS), and defined as the sum of the scores on the Anxiety, Guilt Feelings, Depressive Mood and Hostility items subtracted from the score on the item Blunted affect. When compared with SDS, the PDS showed a sensitivity and specificity rates of 79% and 89%, respectively. The PDS has been used in several investigations aimed at characterizing DS (Kirkpatrick et al., 1996a, 1998, 2000, 2002; Messias and Kirkpatrick, 2001; Subotnik et al., 2000, 1998; Tek et al., 2001; Cohen and Docherty, 2004; Goetz et al., 2007; Strauss et al., 2010). Later on, a proxy measure was derived from the Positive and Negative Syndrome Scale (PANSS) and demonstrated good specificity (78.6%–79.5%) and moderate to very good sensitivity (61.4%–86.4%)(Goetz et al., 2007). However, concerns were raised about the temporal stability and external validity of the proxy measures and caution when employing the PDS in future research is suggested (Subotnik et al., 1998; Roy et al., 2001a; Cohen et al., 2010). In fact, these measures reflect the severity of one negative symptom, i.e. blunted affect, and consider few confounders, but do not take into account negative symptoms clustering into the avolition factor of the SDS (i.e., curbing of interests, diminished sense of purpose and diminished social drive; Galderisi et al., 2013a) and other potential sources of secondary negative symptoms (e.g. extrapyramidal and positive symptoms). The temporal stability seems to be a crucial point as a longitudinal study using the PDS to classify patients could not confirm stability at 1 year follow-up (Subotnik et al., 1998).

A study has further demonstrated that transitory negative symptoms differ markedly from the deficit ones in terms of associations with external validators, such as outcome (Peralta and Cuesta, 2004). According to these findings, the distinction between transitory and persistent negative symptoms is as important as the differentiation of primary vs secondary in defining the deficit syndrome (Peralta and Cuesta, 2004).

2.3. Prevalence, demographic features and risk factors

According to epidemiological data, DS is a rare condition, with a prevalence of 15% in first episode patients, 25–30% in clinical samples and 14–17% in population studies (Kirkpatrick et al., 2000, 2001). An association between DS and male gender has been reported (Carpenter et al., 1988; Bottlender et al., 2001; Roy et al., 2001b). DS is associated with a family history of schizophrenia (Dollfus et al., 1998; Kirkpatrick et al., 2000, 2001; Ross et al., 2000) and an increase in summer births compared with the general population, unlike schizophrenia in general for which a winter birth excess is reported (Kirkpatrick and Galderisi, 2008). Unreplicated associations were also reported between DS and presence of serum antibodies to cytomegalovirus (Dickerson et al., 2006) and low serum folate concentration (Goff et al., 2004).

2.4. Premorbid functioning

Subjects with DS have poorer premorbid adjustment, even after controlling for the severity of negative symptoms (Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009; Bucci et al., 2016). In DS premorbid adjustment is poor in all developmental stages, while in NDS the impairment appears in late adolescence/early adulthood (Buchanan et al., 1990; Galderisi et al., 2002). The early impairment might represent the onset of deficit symptoms (Galderisi and Maj, 2009) or a risk factor for the disorder (Yung et al., 2004; Peralta et al., 2014). A study reported an association of DS with longer duration of untreated psychosis (DUP) (Peralta et al., 2014), in agreement with evidence of a link between DUP and enduring negative symptoms (Edwards et al., 1999; Malla et al., 2004; Chang et al., 2011; Galderisi et al., 2013b).

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