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Mucci, Armida; Merlotti, Eleonora; Ucok, Alp; Aleman, Andre; Galderisi, Silvana

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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).

2.5. Signs and symptoms

As compared with NDS, patients with DS have an insidious onset of the illness more frequently, have more negative symptoms, comparable severity of positive symptoms, and lower prevalence of dysphoria, hostility, suicidal ideation, depressive symptoms and substance abuse (Kirkpatrick et al., 2001; Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009; Kirkpatrick, 2014).

Several studies showed that DS is associated with higher frequency of neurological soft signs (NSS) and spontaneous movement disorders (SMD) than NDS, although there are discrepancies in the type of prevailing abnormalities, probably due to confounding variables, such as the overall negative symptom severity and treatment history, not always controlled for (Fenton et al., 1994; Arango et al., 2000; Kirkpatrick et al., 2001; Galderisi et al., 2002; Tiryaki et al., 2003; Cimmer et al., 2006; Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009; Telfer et al., 2011). Only one study investigated the issue in drug-naïve patients and reported more NSS (motor sequencing) and SMD (excepting akathisia) in DS than in NDS subjects, suggesting common underlying neurobiological mechanisms for DS and these neurological abnormalities (Peralta et al., 2014).

2.6. Neurocognitive impairment

Neuropsychological investigations reported discrepant findings, with some studies reporting a greater impairment in DS than in NDS on measures of fronto-parietal functions (i.e., attention, executive control and visuospatial functions, Buchanan et al., 1994; Bryson et al., 2001; Yu et al., 2015), prefrontal functions (verbal fluency, concept formation and cognitive flexibility, Cascella et al., 2008; Polgár et al., 2010) or cortico-striatal functions (reinforcement learning, Farkas et al., 2008; Polgár et al., 2010; Vogel et al., 2013). The majority of studies (Galderisi et al., 2002, 2013a; Wang et al., 2008; Polgár et al., 2008; Réthelyi et al., 2012; Fervaha et al., 2015a) and a meta-analysis (Cohen et al., 2007) reported a generalized cognitive impairment in DS vs both NDS and controls. Reduced general cognitive abilities in DS might be related to a neurodevelopmental trajectory with early cognitive impairment interfering with the acquisition of subsequent competences (Galderisi et al., 2002). However, the hypothesis awaits further testing.

The relationship between cognitive impairments and deficit symptoms is not clear (Buchanan et al., 2011; Harvey et al., 2006): both are present well before the psychotic decompensation, are more longitudinally stable and have a greater impact on functional outcome than positive symptoms or disorganization (Galderisi et al., 2014; Harvey et al., 2006). Although a common or overlapping pathophysiology has been hypothesized, the extent to which there is a shared pathophysiology has not been clarified (Harvey et al., 2006; Kirkpatrick et al., 2001). Several studies have reported weak relationships between cognitive dysfunctions and negative symptoms, but overall evidence confirmed that the two domains are independent; (Foussias et al., 2014; Galderisi et al., 2014; Harvey et al., 2006). A longitudinal study in DS patients reported that avolition and expressive deficit, as assessed by the SDS, were related to different dimensions of functional outcome with respect to generalized cognitive impairment observed in these patients (Galderisi et al., 2013a). These findings lend support to the hypothesis of the independence of negative symptoms and cognitive impairment.

In the study by Fervaha et al. (2015a) the pattern of generalized cognitive impairment in DS was found to be related to the presence of negative symptoms in the clinical picture, irrespective of their primary nature; in fact, comparing DS with a subgroup of NDS subjects with negative symptoms did not reveal any difference between the two groups. Since poor motivation in subjects with negative symptoms might confound the results of neuropsychological assessment due to inadequate mental effort (Gorissen et al., 2005; Avery et al., 2009; Strauss et al., 2015), Morra et al. (2015) investigated the relationships of DS categorization and negative symptom severity with mental effort and general cognitive abilities (IQ). They confirmed the association of negative symptoms with poor mental effort (Gorissen et al., 2005; Avery et al., 2009; Strauss et al., 2015) and reported that patients showing inadequate mental effort had an increased likelihood of being affected by DS and showing low IQ. This pattern of findings did not clarify whether the generalized impairment reflects motivational problems or genuine cognitive deficits. The measure used in this study was designed to capture inadequate effort in populations with a less generalized neurocognitive impairment (Morra et al., 2015), while in DS both generalized cognitive deficits and severe motivational problems are probably in play. To clarify the issue, future studies should include large samples of DS and NDS with a wider range of IQ values and negative symptom severity than the ones reported in previous studies. More recently, the use of performance-based assessment tools to measure motivational deficits has become a focus of investigation (Fervaha et al., 2013; Barch et al., 2014; Hartmann et al., 2015). Fervaha et al. (2015b) used an effort-based decision making task and found that DS exerted effort for reward at a significantly lower rate than NDS. No correlation between performance at this task and negative symptoms was observed, suggesting that the deficit classification yields information in addition to negative symptoms ratings. The performance on the task was not associated with an index of general cognitive functioning (based on the Letter-Number Sequencing and Digit-Symbol substitution tests). These results suggest that motivation problems and cognitive dysfunction are independent domains of impairment in DS.

2.7. Electrophysiological investigations

While a number of studies examined the electrophysiological correlates of negative symptoms in schizophrenia (Boutros et al., 2014), few studies focused on DS. The indices investigated in DS include: 1) P50, an index of sensory gating; 2) mismatch negativity (MMN) a measure of automatic pre-attentive processes of stimuli monitoring; 3) P100 and N100, indices of early sensory and attention processes; 4) the N2 and P3, indices of effortful processing and task-relevance; 5) contingent negative variation (CNV) and post-imperative negative variation (PINV), components related to anticipation and orienting to upcoming stimuli and response preparation, as well as 6) oculomotor functions, i.e. smooth pursuit eye movements and visual reaction time.

Turetsky et al. (1998) found that, with respect to healthy controls, NDS had reduced amplitude for all P3 subcomponents (left temporal, right parietal and frontal, with greater reduction of the left temporal one), while DS presented a reduced amplitude of two subcomponents (right parietal and left temporal, with a more severe abnormality of the right parietal one). The authors used a proxy measure to characterize DS subjects. Mucci et al. (2007) found a double dissociation in event-related potentials showing that, compared to healthy controls, DS but not NDS had reduced N1 amplitude and current source density, while NDS but not DS had P3 topography and current source density abnormalities, as well as a reduction of global field power (a reference-free measure of amplitude). The two patient groups also differed from each other on the same measures. Both studies found that the pattern of abnormalities in NDS was similar to the one generally observed in schizophrenia, while the pattern found in DS had a qualitative divergence from it, suggesting that DS and NDS represent different disease entities.

Santos et al. (2010) did not find differences between the DS and NDS in P50 gating; Li et al. (2013) investigated N1, N2, P3 (both P3a and P3b subcomponents, indexing automatic attention allocation and effortful processing, respectively), MMN, P50 and the CNV in DS and NDS. The two subgroups shared most abnormalities; however, with respect to healthy controls, PINV latency was delayed in NDS and shortened in DS; furthermore, a delayed latency was found only in NDS for P3b and only in DS for the CNV expectancy wave. The same research group has recently investigated CNV and PINV in DS and matched psychotic bipolar patients and reported that only DS had a reduced latency of PINV and

an increased latency of CNV (Li et al., 2015). As to frequency analysis of ERP data, only one EEG investigation addressed induced gamma activity in DS and NDS patients and found a reduction of induced gamma power only in the latter group (Bucci et al., 2007).

On the whole the pattern of ERP results suggests an impairment of processes related to early attention, expectation and response preparation in DS as compared with NDS. At odds with consolidated findings in subjects with schizophrenia, no impairment of P300 was found in DS. The qualitative divergence of findings suggests that DS and NDS represent different disease entities.

More pronounced oculomotor dysfunction associated with poor sensory integration (Ross et al., 1996, 1997, 1998; Bustillo et al., 1997) was reported in DS and their relatives, with respect to NDS, in earlier studies. A later investigation (Nkam et al., 2001) confirmed the presence of severe abnormalities in DS, using different oculomotor indices; however, both DS and NDS significantly differ from controls on the same indices. Furthermore, Malaspina et al. (2002) reported an association between oculomotor abnormalities and DS that was no more significant after controlling for the association of DS with a deficit in olfactory identification (an index of limbic dysfunction) which was associated with both oculomotor abnormalities and DS status. Another study used an original paradigm to disentangle predictive smooth pursuit deficits (showing an association with positive symptoms) from deficits in initiation of eye movements which resulted to be associated with DS and the liability to the syndrome (Hong et al., 2003). However, a more recent study using a similar paradigm (Nkam et al., 2010) did not confirm the association of either abnormality with DS. At the moment, no conclusion can be drawn from these studies due to the heterogeneity of employed paradigms and measured indices as well as to small average sample size.

2.8. Structural and functional brain imaging findings

Findings from structural brain imaging studies investigating differences in gray and/or white matter volume or density in DS versus NDS and healthy controls have been mixed. Buchanan et al. (1993) found that patients with NDS (N = 24) had smaller prefrontal volumes with respect to controls and to patients with DS (N = 17), while the latter did not differ from controls. Similar findings were more recently reported by an independent group (Volpe et al., 2012), who found greater reduction of the dorsolateral prefrontal cortex in NDS as compared to DS patients.

Several studies reported greater abnormalities in the temporal lobe in DS than in NDS patients. Turetsky et al. (1995) reported abnormal temporal lobe asymmetry only in patients with DS (N = 21), who showed a selective increase in left temporal lobe cerebrospinal fluid (CSF) volume in comparison with both NDS (N = 49) patients and healthy controls. Galderisi et al. (2008) studied 34 patients with DS, 32 with NDS, and 31 healthy comparison subjects. DS patients had significantly smaller right temporal lobe volume as compared with NDS patients, while NDS, but not DS patients, had larger lateral ventricles than control subjects. Both patient groups had smaller dorsolateral prefrontal cortex and temporal lobes than healthy subjects.

Two further studies found evidence of gray matter reduction in the temporal lobe in DS with respect to both healthy controls and NDS (involving the superior temporal gyrus in one case, Cascella et al., 2010; and the superior and middle temporal gyrus in the other paper, Fisher et al., 2012).

Cortical thickness was evaluated by Voineskos et al. (2013) in 18 patients with DS, 59 patients with NDS, and 79 healthy controls. They did not find any difference between DS and NDS patients and both groups had reduced thickness compared with healthy controls.

A recent study investigated network-level properties of cortical thickness, assessing interregional coupling and network parameters of cortex in DS, NDS, healthy controls and bipolar I patients (Wheeler et al., 2015). Results showed enhanced interregional coupling, associated with high regional centrality in the inferior frontal, inferior parietal, and middle and superior temporal cortices, in DS patients with respect to the other groups. The pattern of results was contrary to findings of previous investigations using network-based analysis in other groups of schizophrenia patients suggesting reduced frontotemporal and frontoparietal connectivity (Bassett et al., 2008; Skudlarski et al., 2010; Zalesky et al., 2011; Fornito et al., 2012). Wheeler et al. (2015) therefore concluded that DS patients may represent a subset of people with schizophrenia who experience early-onset alterations that may interfere with basic socio-cognitive skills. Increased network density may reflect decreased differentiation of networks during development.

On the basis of these findings concerning gray matter abnormalities, DS does not appear as just the extreme end of a severity continuum within schizophrenia.

Several studies reported white matter abnormalities in DS, especially in frontoparietal and frontotemporal circuitry (Rowland et al., 2009; Kitis et al., 2012). Voineskos et al. (2013), in the same MRI structural study summarized above for the gray matter findings, investigated also diffusion-based measures of white matter tracts. DS patients exhibited disruption of white matter tracts including the inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus compared to both healthy controls and NDS, suggesting a possible link between these abnormalities and the emotional and social dysfunctions reported in DS patients. Spalletta et al. (2015) compared microstructural diffusion-related parameters as measured by diffusion tensor imaging in 21 DS, 21 NDS, and 21 healthy controls. Fractional anisotropy was reduced in the right precentral area in NDS patients, and in the left corona radiata of the schizophrenia group as a whole. Axial diffusivity was reduced in the left postcentral area of DS patients, whereas radial diffusivity was increased in the left forceps minor of DS patients and in the left internal capsule of NDS patients.

Thus, as was concluded for patterns of gray matter alterations, DS patients are not simply at the extreme end of a severity continuum of white matter disruption.

As to functional brain imaging investigations, only few studies were carried out in DS patients.

Earlier studies reported a decrease of glucose metabolism or cerebral blood flow in the frontal (Gonul et al., 2003; Heckers et al., 1999; Lahti et al., 2001; Tamminga et al., 1992; Vaiva et al., 2002) and parietal regions (Gonul et al., 2003; Lahti et al., 2001; Tamminga et al., 1992) in DS versus NDS and healthy controls.

In a functional magnetic resonance (fMRI) study of reward processing (using a monetary incentive delay task), Mucci et al. (2015a) observed a significant reduction of dorsal caudate activity during reward anticipation in DS patients as compared with both healthy controls and NDS patients. The dorsal caudate activity was inversely related to avolition as measured by the SDS. The relationship of dorsal caudate dysfunction with avolition/apathy as measured by SANS was recently confirmed (Morris et al., 2015). The dorsal caudate is involved in forming associations between action and reward, thus the above data seem to indicate that DS (especially when characterized by avolition) is associated to an impairment in valuing own actions based on the achievement of a reward.

2.9. Psychosocial functioning and response to treatment

Patients with DS have poorer psychosocial functioning than those with NDS both before the appearance of positive symptoms and later on in the course of the illness, even when controlling for demographic variables (such as older age), greater anxiety, depressed mood and severity of positive symptoms and disorganization (Fenton and McGlashan, 1994; Kirkpatrick et al., 1993, 1994, 2001; Tek et al., 2001; Strauss et al., 2010; Galderisi et al., 2013a; Peralta et al., 2014), as well as antipsychotic medication (Kirkpatrick and Galderisi, 2008; Galderisi and Maj, 2009; Peralta et al., 2014) or substance abuse (Kirkpatrick et al., 1996a, 1996b).

A clinical trial that used the SDS to define DS and NDS groups, reported no improvement in the negative symptoms of patients with DS using clozapine (Breier et al., 1994); in the 1-year follow-up of the same subjects, clozapine did not have any superior efficacy with respect to haloperidol or long-term effect on primary or secondary negative symptoms in DS (Buchanan et al., 1998). In line with these results, Rosenheck et al. (1999) reported that over a one year period there was no effect of clozapine on enduring negative symptoms. A systematic review concluded that studies investigating the effects of clozapine on primary and enduring negative symptoms do not provide conclusive evidence of its efficacy (Murphy et al., 2006).

According to a meta-analysis (Leucht et al., 2002), among atypical antipsychotics, amisulpride demonstrated an effect on deficit symptoms, especially at low doses. However, the drug was significantly superior to placebo, but not to conventional antipsychotics (Leucht et al., 2002). Furthermore, none of the placebo-controlled studies included in this meta-analysis used the SDS for the diagnosis of DS. Vaiva et al. (2002), in a small sample of patients categorized as having DS or NDS using the SDS, reported that the efficacy of amisulpride was higher in patients with NDS than in those with DS, suggesting an effect on secondary negative symptoms.

Two studies have examined the effects of olanzapine on negative symptoms in patients diagnosed as having DS using the SDS (Kopelowicz et al., 2000; Lindenmayer et al., 2007). The first study found an improvement of positive, negative and extrapyramidal symptoms in NDS and of extrapyramidal symptoms only in DS (Kopelowicz et al., 2000), suggesting an effect of olanzapine limited to the secondary negative symptoms. The second study reported higher efficacy of olanzapine, with respect to haloperidol, on primary negative symptoms (Lindenmayer et al., 2007); however this study did not include an NDS control group.

Möller et al. (2004) found that zotepine induced a marked improvement of primary negative symptoms, but the drug was not discriminated from placebo.

Several studies examined the efficacy of adjunctive treatment on negative symptoms (Arango et al., 2013; Fusar-Poli et al., 2015). A few of these studies examined the effects on enduring negative symptoms of antipsychotic augmentation with N-methyl-D-aspartate (NMDA) receptor-stimulating agents, such as glycine, D-serine or D-cycloserine (Goff et al., 1995, 1999; Heresco-Levy et al., 1999; Buchanan et al., 2007). However, the only study which assessed the effects of adjunctive glycine or D-cycloserine (versus placebo) in DS and NDS subjects (categorized using the SDS) did not find any significant improvement of primary negative symptoms (Buchanan et al., 2007).

3. Persistent negative symptoms

3.1. Definition

The concept of PNS is broader than that of DS (Buchanan, 2007) and, according to the NIMH-MATRICS consensus report, includes symptoms that have not responded to the usual treatments, interfere with patient's ability to perform normal role functions, persist during periods of clinical stability, and represent an unmet therapeutic need (Kirkpatrick et al., 2006). PNS criteria according to Buchanan (2007) are listed in Box 2.

3.1.1. Relationships with other definitions used in clinical trials: prominent and predominant negative symptoms.

Regulatory agencies and expert panels agreed on the definition of ideal populations to be included in clinical studies aimed to demonstrate an effect on negative symptoms. Two definitions have been used (Kinon et al., 2006; Rabinowitz et al., 2013; Stauffer et al., 2012) to identify a population with clinically-relevant negative symptoms: prominent and predominant negative symptoms (Kinon et al., 2006; Rabinowitz et al., 2013; Stauffer et al., 2012). Criteria were based on the PANSS scores and identified different patient populations.

Box 2
Criteria for definition of persistent negative symptoms (Buchanan, 2007).

a) Presence of at least moderate severity of negative symptoms, defined on an accepted and validated rating scale;
b) defined threshold levels of positive symptoms, depression and extrapyramidal symptoms on accepted and validated rating scales;
c) persistence for at least 6 months.

Prominent negative symptoms were defined as (1) Baseline score ≥4 (moderate) on at least three, or ≥5 (moderately severe) on at least two negative PANSS subscale items (Kinon et al., 2006; Stauffer et al., 2012; Rabinowitz et al., 2013). The definitions of predominant negative symptoms were more heterogeneous and included: (1) the same severity threshold for the PANSS negative subscale as for prominent negative symptoms, plus a PANSS positive score of less than 19 (Stauffer et al., 2012); (2) PANSS negative subscale score at least 6 points higher than the PANSS positive subscale score (Olie et al., 2006); (3) PANSS negative subscale score of at least 21 and at least 1 point greater than the PANSS positive subscale (Riedel et al., 2005) and (4) a common sense definition: PANSS negative subscale greater than the positive one (Rabinowitz et al., 2013). Thus, the definition of the predominant negative symptoms is characterized by the reduced severity of the positive symptomatology with respect to the negative one. Stauffer et al. (2012) also included a threshold for the depressive and extrapyramidal symptomatology, as assessed by standard scales. With the exception of the latter definition, the prominent and predominant definitions have very limited overlap with the construct of PNS and include a mixture of primary and secondary negative symptoms with possible large fluctuation over time. A revision of these criteria in guidelines and regulatory agencies requirements was advocated by panels of experts (Marder et al., 2011; Marder and Kirkpatrick, 2014). As a matter of fact, instability over time of the negative symptoms might confound the results of clinical trials by increasing the proportion of subjects improving on the control condition and can confound research findings by increasing the variability of both experimental and control conditions (Marder et al., 2011; Marder and Kirkpatrick, 2014). The PNS construct thus represents a clear improvement in the definition of the target population for clinical trials and research on pathophysiology of negative symptoms.

3.2. Assessment

PNS definition requires the presence of negative symptoms of at least moderate severity. An accepted and validated rating scale like the PANSS, the Scale for the Assessment of Negative Symptoms (SANS), the Negative Symptom Assessment Scale (NSA) or more recent, validated instruments like the Brief Negative Symptom Scale (BNSS, Kirkpatrick et al., 2011; Mucci et al., 2015b) and the Clinical Assessment Inventory for Negative Symptoms (CAINS, Kring et al., 2013) can be used. Repeated assessments (i.e. every 3–6 months) are recommended to make sure that negative symptoms persist. Persistence for at least 6 months is required (Buchanan, 2007).

Different studies have used heterogeneous criteria for the assessment of PNS: persistence of at least one negative symptom above the threshold in two repeated assessments (Malla et al., 2004; Hovington et al., 2012; Galderisi et al., 2013b), or at least two supra-threshold negative symptoms, or persistence of the same symptoms in more than 2 repeated assessments (Hovington et al., 2012; Üçok and Ergül, 2014). The assessment of PNS should take into account the most frequent and measurable causes of secondary negative symptoms. Positive, depressive and extrapyramidal symptoms should be lower than a defined threshold on an accepted and validated rating scale. PANSS positive subscale, the Scale for Assessment of Positive Symptoms (SAPS) or BPRS

positive symptom subscale can be used to assess the severity of positive symptoms. Patients may be required to have a global rating of mild or less on all positive symptoms. A total score of 6 (Galderisi et al., 2013b) or 4 (Hovington et al., 2012) on the Calgary Depression Scale for Schizophrenia (Addington et al., 1993), or <6 on the Depression subscale of BPRS (Üçok and Ergül, 2014) are frequently used thresholds for depression. Simpson-Angus Extrapyramidal Rating Scale, Extrapyramidal Symptom Rating Scale, St Hans Rating Scale have been used to exclude supra-threshold extrapyramidal symptoms; absence or a threshold of mild for parkinsonism has usually been adopted.

3.3. Prevalence and demographic features

There is a great variability in the reported prevalence rates of PNS due to differences in its definition and characteristics of study samples. Epidemiological data pertaining to PNS are sparse. In the light of the estimated 15%–20% prevalence of DS, the prevalence of PNS is probably higher because the latter might also include unresponsive secondary negative symptoms (Buchanan, 2007). Reported rates of PNS in first-episode psychosis samples were between 3.8 and 31.5% at one-year follow-up (Mayerhoff et al., 1994; Edwards et al., 1999; Malla et al., 2004; Chang et al., 2011; Hovington et al., 2012; Galderisi et al., 2013b; Üçok and Ergül, 2014). According to three recent studies prospective consistency of negative symptoms from baseline to 12 months is between 16 and 35% (Chang et al., 2011; Galderisi et al., 2013b; Üçok and Ergül, 2014). Studying PNS early in the course of schizophrenia may be advantageous as there are less confounding variables (e.g. side effects of antipsychotics, social isolation, stigma and multiple relapses) in this population than in chronic patients.

3.4. Risk factors

Duration of untreated psychosis (DUP) was consistently found in association with PNS and might be considered as a risk factor (Edwards et al., 1999; Malla et al., 2004; Chang et al., 2011; Galderisi et al., 2013b; Gonzalez-Valderrama et al., 2015). It might be hypothesized that the association reflects insidious onset of psychosis as well as delayed presentation and access to treatment in patients in which negative symptoms prevail in the clinical picture. Evidence has been provided that DUP reduction markedly decreases distress and disability, persistently improves negative symptoms at 5 years and doubles the rate of recovery (31 vs. 15%) at 10 years (Larsen et al., 2011; Ten Velden Hegelstad et al., 2013).

3.5. Premorbid functioning and other demographic and clinical correlates

PNS are associated with poor premorbid functioning (Edwards et al., 1999; Malla et al., 2004; Chang et al., 2011; Üçok and Ergül, 2014) and male gender (Chang et al., 2011). Subjects with PNS versus those without PNS have lower quality of life and real-life functioning, worse vocational outcome, less adherence to treatment, and higher levels of symptoms at follow-up (Edwards et al., 1999; Malla et al., 2004; Chang et al., 2011; Hovington et al., 2012, Galderisi et al., 2013b; Üçok and Ergül, 2014). Studies with longer than one year follow-up periods are also recommended because PNS prevalence and relationship with functioning may change over time (Chang et al., 2011; Ayesa-Arriola et al., 2013).

3.6. Neurocognitive functioning

Neurocognitive functioning in subjects with PNS versus those without PNS was analyzed in four FEP studies; no difference was found between the two groups in two of them (Chang et al., 2011; Galderisi et al., 2013b); one study reported a worse performance on executive functioning and attention tests at baseline in patients with PNS (Üçok and Ergül, 2014) and another one (Hovington et al., 2013) found a greater verbal memory impairment in the PNS group, which was stable over time (12 month-follow-up). In the latter study, the verbal memory impairment was associated with the severity of alogia. Thus it is possible that the persistence of different dimensions of negative symptoms is associated with different patterns of cognitive impairment: the hypothesis awaits further longitudinal studies.

3.7. Structural and functional brain imaging

A recent review on structural and functional brain abnormalities in subjects with or without PNS concluded that gray matter reductions in the temporal lobe and white matter alterations in the frontal lobe may be related to PNS (Hovington and Lepage, 2012). In first-episode patients with schizophrenia-spectrum disorders a recent study (Bodnar et al., 2014) reported that cortical thinning was more marked in subjects with PNS versus those without PNS in the right superior temporal gyrus (extending to the temporo-parietal junction), right parahippocampal gyrus and left orbital frontal gyrus. With respect to healthy controls, patients with PNS showed thinner cortex in the right superior temporal and right parahippocampal regions, while those without PNS in bilateral parahippocampal gyrus. These abnormalities might be the basis of impaired social functioning in subjects with PNS.

No study has specifically addressed functional brain imaging correlates of PNS. Using PET-scans of regional glucose metabolism, Lubeiro et al. (2016) found reduced thalamic and cingulate glucose metabolism in comparison to controls, in a subgroup of schizophrenia patients that showed persistence/worsening of negative symptoms at follow-up. However, criteria for PNS were not applied and the confounding role of EPS, depression or residual positive symptoms was not assessed.

3.8. Course and outcome

A worse global functioning after 1 year of treatment and poor daily functioning in first-episode patients with PNS was consistently reported, demonstrating that early in the course of the illness PNS predict poor psychosocial functioning (Milev et al., 2005; Evensen et al., 2012; Hovington et al., 2012; Galderisi et al., 2013b; Chang et al., 2013; Ventura et al., 2015).

The motivation domain of negative symptoms (anhedonia, asociality and avolition) has been associated with poor functional outcome more than the expressive domain (alogia and affective flattening) in most investigations (Malla et al., 2002; Atbaşoglu et al., 2003; Blanchard et al., 2005; Avery et al., 2009; Galderisi et al., 2013a, 2014). According to some authors, the majority of patients met the PNS criteria due to elevated scores on either the avolition or anhedonia/asociality domains of the negative symptoms, suggesting a key role of the latter symptoms in the clinical presentation of PNS and in its association with poor functional outcome (Foussias and Remington, 2010; Hovington et al., 2012).

4. Conclusions

In the last decades, the attempt to reduce heterogeneity of negative symptoms of schizophrenia led to the identification of two psychopathological constructs: DS and PNS.

Since the introduction of the criteria for diagnosing DS a large body of research has been carried out, trying to distinguish DS from NDS. An important research question is whether DS represents a more severe form of the same illness with respects to NDS or a separate disease entity. Brain imaging (Gonul et al., 2003; Heckers et al., 1999; Lahti et al., 2001; Tamminga et al., 1992; Vaiva et al., 2002; Quarantelli et al., 2002; Galderisi et al., 2008; Volpe et al., 2012; Voineskos et al., 2013; Mucci et al., 2015a; Spalletta et al., 2015; Wheeler et al., 2015), electrophysiological (Ludewig and Vollenweider, 2002; Bucci et al., 2007; Mucci et al., 2007; Fisher et al., 2012; Li et al., 2013), and oculomotor data (Ross et al., 1996, 1997, Hong et al., 2003), showing either less or different abnormalities in patients with DS with respect to those with

NDS, suggest that DS represents a separate disease entity with respect to other forms of schizophrenia, and not just the extreme end of a severity continuum. The evidence that DS and NDS have different risk factors (Dollfus et al., 1998; Kirkpatrick et al., 2002, 2006; Messias et al., 2004; Dickerson et al., 2006; Gallagher et al., 2007; Kallel et al., 2007) and recent taxometric/latent class analyses further support this hypothesis (Blanchard et al., 2005; Ahmed et al., 2015). Most findings, however, await replication. Moreover, although interesting findings have been provided by subdividing patients into DS and NDS, it should be highlighted that subjects with DS may still have secondary negative symptoms, and the different weight of the latter ones in different groups of patients may produce some heterogeneity. Furthermore, the most recent latent class analysis, carried out in a large sample of subjects (Ahmed et al., 2015), reported that although there was evidence of a separable class of individuals with enduring and idiopathic negative symptoms, a hybrid categorical-dimensional structure was also supported (Ahmed et al., 2015) as enduring negative symptoms, non necessarily idiopathic, were significantly associated with the same variables as the identified taxon and DS. In the light of these observations, while the PNS construct was proposed for clinical trials aimed to test new treatments, it should be considered a viable construct to promote research also on pathophysiology of negative symptoms intrinsic to the disease process. The few studies investigating the presence of the deficit syndrome (using the SDS) in samples of patients with non-schizophrenic disorders (Gerbaldo et al., 1997; Peralta and Cuesta, 2004), reported that enduring negative symptoms occur also in disorders other than schizophrenia (in 2-22% of the non-schizophrenic psychosis, Peralta and Cuesta, 2004). In the latter study, the presence of enduring negative symptoms per se was associated to poor outcome and risk factors generally observed for DS. As reviewed in the present paper, key findings concerning risk factors and associations with external validators seem to indicate that PNS and DS share several characteristics relevant to pathophysiological models of enduring negative symptoms. The association of both DS and PNS with poor premorbid adjustment and DUP might indicate a relationship with early neurodevelopmental abnormalities and a progression due to neurobiological changes occurring after the onset of psychosis. The association of DS with reduced general cognitive abilities, neurological soft signs and movement disorders lends further support to the hypothesis of pervasive neurodevelopmental abnormalities (Peralta et al., 2014). Recent findings of increased network density only in DS patients, which might reflect decreased differentiation of networks during development, would strengthen this hypothesis. In this perspective, early-onset alterations of experience-dependent plasticity would interfere with structural and functional connectivity subserving the acquisition of basic neurological and socio-cognitive skills in DS (Galderisi et al., 2002; Galderisi et al., 2008; Peralta et al., 2014; Wheeler et al., 2015). The onset of psychosis might add to this altered connectivity producing a further impairment in brain plasticity related to abnormal salience attribution to stimuli and events with no intrinsic reward value (Horga et al., 2016; Howes and Kapur, 2009). If PNS and DS are the results of pervasive neurodevelopmental disorders, the implication for treatment are complex: a combination of psychosocial rehabilitation programs and techniques to improve brain plasticity should be implemented to favor the development of never-acquired functions and facilitate experience-dependent plastic changes to re-shape functional and structural connectivity within relevant networks.

Factor analyses and experimental studies suggest that even primary and persistent negative symptoms include different psychopathological domains, i.e., avolition and diminished expression. A study using both a categorical and dimensional approach to characterize functional imaging correlates of enduring negative symptoms (Mucci et al., 2015a) reported that DS and avolition, but not expressive deficit, was associated with a reduction of dorsal caudate activity during reward anticipation. Both animal and human experimental data suggest that the dorsal striatum has a prominent role in motivation (Balleine and O'Doherty, 2010; Miller et al., 2014; Morris et al., 2015; Palmiter, 2008). A reduced ventral striatal activation during anticipation of reward (Kirschner et al., 2016; Radua et al., 2015) has also been reported in patients with anhedonia and avolition. However, these studies did not characterize avolition and anhedonia as enduring, and the relevance of these findings to PNS or DS is not clear. A refinement of the hypothesis concerning the avolition dimension of enduring negative symptoms heavily depends on studies including subjects with persistent avolition and anhedonia. Pathophysiological models of expressive deficit were not explored in subjects with either DS or PNS.

In conclusion, studies using both categorical and dimensional approaches and a longitudinal design are needed to refine hypotheses concerning enduring negative symptoms, whose treatment remains an unmet need of schizophrenia. The association of both DS and PNS with poor long-term outcome requires a focused and dedicated effort to unravel their pathophysiology thus contributing to the development of new treatments.

Authors' contributions

All authors were involved in the manuscript development and review and have approved the final draft of the manuscript for publication.

Conflicts of interest

Armida Mucci has received a partial coverage of the expenses to participate in the 2015 EPA congress from Janssen-Cilag (unrelated to this paper).

Alp Üçok has received honoraria from Abdi Ibrahim, Otsuka, AstraZeneca and Janssen-Cilag (unrelated to this paper).

Silvana Galderisi participated in advisory boards for Hoffmann-La Roche, Janssen-Cilag, Lundbeck, Angelini-Acraf, Amgen and Pierre Fabre (unrelated to this paper).

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Eleonora Merlotti has no conflict of interest to declare.

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References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. Br. J. Psychiatry Suppl. 22, 39–44.

Ahmed, A.O., Strauss, G.P., Buchanan, R.W., Kirkpatrick, B., Carpenter, W.T., 2015. Are negative symptoms dimensional or categorical? Detection and validation of deficit schizophrenia with taxometric and latent variable mixture models. Schizophr. Bull. 41 (4), 879–891.

Amador, X.F., Kirkpatrick, B., Buchanan, R.W., Carpenter, W.T., Marcinko, L., Yale, S.A., 1999. Stability of the diagnosis of deficit syndrome in schizophrenia. Am. J. Psychiatry 156 (4), 637–639.

Arango, C., Kirkpatrick, B., Buchanan, R.W., 2000. Neurological signs and the heterogeneity of schizophrenia. Am. J. Psychiatry 157 (4), 560–565.

Arango, C., Garibaldi, G., Marder, S.R., 2013. Pharmacological approaches to treating negative symptoms: a review of clinical trials. Schizophr. Res. 150 (2-3), 346–352.

Atbaşoglu, E.C., Ozgüven, H.D., Olmez, S., 2003. Dissociation between inattentiveness during mental status testing and social inattentiveness in the Scale for the Assessment of Negative Symptoms attention subscale. Psychopathology 36 (5), 263–268.

Avery, R., Startup, M., Calabria, K., 2009. The role of effort, cognitive expectancy appraisals and coping style in the maintenance of the negative symptoms of schizophrenia. Psychiatry Res. 167 (1-2), 36–46.

Ayesa-Arriola, R., Rodríguez-Sánchez, J.M., Pérez-Iglesias, R., González-Blanch, C., Pardo-García, G., Tabares-Seisdedos, R., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2013. The relevance of cognitive, clinical and premorbid variables in predicting functional outcome for individuals with first-episode psychosis: a 3 year longitudinal study. Psychiatry Res. 209 (3), 302–308.

Balleine, B.W., O'Doherty, J.P., 2010. Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology 35 (1), 48–69.

Barch, D.M., Treadway, M.T., Schoen, N., 2014. Effort, anhedonia, and function in schizophrenia: reduced effort allocation predicts amotivation and functional impairment. J. Abnorm. Psychol. 123 (2), 387–397.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. 28 (37), 9239–9248.

Blanchard, J.J., Horan, W.P., Collins, L.M., 2005. Examining the latent structure of negative symptoms: is there a distinct subtype of negative symptom schizophrenia? Schizophr. Res. 77 (2-3), 151–165.

Bodnar, M., Hovington, C.L., Buchy, L., Malla, A.K., Joober, R., Lepage, M., 2014. Cortical thinning in temporo-parietal junction (TPJ) in non-affective first-episode of psychosis patients with persistent negative symptoms. PLoS One 9 (6), e101372.

Bottlender, R., Jäger, M., Groll, C., Strauss, A., Möller, H.J., 2001. Deficit states in schizophrenia and their association with the length of illness and gender. Eur. Arch. Psychiatry Clin. Neurosci. 251 (6), 272–278.

Boutros, N.N., Mucci, A., Vignapiano, A., Galderisi, S., 2014. Electrophysiological aberrations associated with negative symptoms in schizophrenia. Curr. Top. Behav. Neurosci. 21, 129–156.

Breier, A., Buchanan, R.W., Kirkpatrick, B., Davis, O.R., Irish, D., Summerfelt, A., Carpenter Jr., W.T., 1994. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am. J. Psychiatry 151 (1), 20–26.

Bryson, G., Whelahan, H.A., Bell, M., 2001. Memory and executive function impairments in deficit syndrome schizophrenia. Psychiatry Res. 102 (1), 29–37.

Bucci, P., Mucci, A., Merlotti, E., Volpe, U., Galderisi, S., 2007. Induced gamma activity and event-related coherence in schizophrenia. Clin. EEG Neurosci. 38 (2), 96–104.

Bucci, P., Mucci, A., Piegari, G., Nobile, M., Pini, S., Rossi, A., Vita, A., Galderisi, S., Maj, M., 2016. Characterization of premorbid functioning during childhood in patients with deficit vs. non-deficit schizophrenia and in their healthy siblings. Schizophr. Res. (Epub ahead of print).

Buchanan, R.W., 2007. Persistent negative symptoms in schizophrenia: an overview. Schizophr. Bull. 33 (4), 1013–1022.

Buchanan, R.W., Kirkpatrick, B., Heinrichs, D.W., Carpenter Jr., W.T., 1990. Clinical correlates of the deficit syndrome of schizophrenia. Am. J. Psychiatry 147 (3), 290–294.

Buchanan, R.W., Breier, A., Kirkpatrick, B., Elkashef, A., Munson, R.C., Gellad, F., Carpenter Jr., W.T., 1993. Structural abnormalities in deficit and nondeficit schizophrenia. Am. J. Psychiatry 150 (1), 59–65.

Buchanan, R.W., Strauss, M.E., Kirkpatrick, B., Holstein, C., Breier, A., Carpenter Jr., W.T., 1994. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. Arch. Gen. Psychiatry 51 (10), 804–811.

Buchanan, R.W., Breier, A., Kirkpatrick, B., Ball, P., Carpenter Jr., W.T., 1998. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am. J. Psychiatry 155 (6), 751–760.

Buchanan, R.W., Javitt, D.C., Marder, S.R., Schooler, N.R., Gold, J.M., McMahon, R.P., Heresco-Levy, U., Carpenter, W.T., 2007. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. Am. J. Psychiatry 164 (10), 1593–1602.

Buchanan, R.W., Keefe, R.S., Umbricht, D., Green, M.F., Laughren, T., Marder, S.R., 2011. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr. Bull. 37 (6), 1209–1217.

Bustillo, J.R., Thaker, G., Buchanan, R.W., Moran, M., Kirkpatrick, B., Carpenter, W.T., 1997. Visual information-processing impairments in deficit and nondeficit schizophrenia. Am. J. Psychiatry 154 (5), 647–654.

Carpenter Jr., W.T., Heinrichs, D.W., Wagman, A.M., 1988. Deficit and nondeficit forms of schizophrenia: the concept. Am. J. Psychiatry 145 (5), 578–583.

Cascella, N.G., Testa, S.M., Meyer, S.M., Rao, V.A., Diaz-Asper, C.M., Pearlson, G.D., Schretlen, D.J., 2008. Neuropsychological impairment in deficit vs. non-deficit schizophrenia. J. Psychiatr. Res. 42 (11), 930–937.

Cascella, N.G., Fieldstone, S.C., Rao, V.A., Pearlson, G.D., Sawa, A., Schretlen, D.J., 2010. Gray-matter abnormalities in deficit schizophrenia. Schizophr. Res. 120 (1-3), 63–70.

Chang, W.C., Hui, C.L., Tang, J.Y., Wong, G.H., Lam, M.M., Chan, S.K., Chen, E.Y., 2011. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr. Res. 133 (1-3), 22–28.

Chang, W.C., Ming Hui, C.L., Yan Wong, G.H., Wa Chan, S.K., Ming Lee, E.H., Hai Chen, E.Y., 2013. Symptomatic remission and cognitive impairment in first-episode schizophrenia: a prospective 3-year follow-up study. J. Clin. Psychiatry 74 (11), 1046–1053.

Cimmer, C., Szendi, I., Csifcsák, G., Szekeres, G., Ambrus Kovács, Z., Somogyi, I., Benedek, G., Janka, Z., Kéri, S., 2006. Abnormal neurological signs, visual contrast sensitivity, and the deficit syndrome of schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 30 (7), 1225–1230.

Cohen, A.S., Docherty, N.M., 2004. Deficit versus negative syndrome in schizophrenia: prediction of attentional impairment. Schizophr. Bull. 30 (4), 827–835.

Cohen, A.S., Saperstein, A.M., Gold, J.M., Kirkpatrick, B., Carpenter Jr., W.T., Buchanan, R.W., 2007. Neuropsychology of the deficit syndrome: new data and meta-analysis of findings to date. Schizophr. Bull. 33 (5), 1201–1212.

Cohen, A.S., Brown, L.A., Minor, K.S., 2010. The psychiatric symptomatology of deficit schizophrenia: a meta-analysis. Schizophr. Res. 118 (1-3), 122–127.

Dickerson, F., Kirkpatrick, B., Boronow, J., Stallings, C., Origoni, A., Yolken, R., 2006. Deficit schizophrenia: association with serum antibodies to cytomegalovirus. Schizophr. Bull. 32 (2), 396–400.

Dollfus, S., Germain-Robin, S., Chabot, B., Brazo, P., Delamillieure, P., Langlois, S., van der Eist, A., Campion, D., Petit, M., 1998. Family history and obstetric complications in deficit and non-deficit schizophrenia: preliminary results. Eur. Psychiatry 13 (5), 270–272.

Edwards, J., McGorry, P.D., Waddell, F.M., Harrigan, S.M., 1999. Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. Schizophr. Res. 40 (2), 147–158.

Evensen, J., Røssberg, J.I., Barder, H., Haahr, U., Hegelstad, W.T., Joa, I., Johannessen, J.O., Larsen, T.K., Melle, I., Opjordsmoen, S., Rund, B.R., Simonsen, E., Sundet, K., Vaglum, P., Friis, S., McGlashan, T., 2012. Apathy in first episode psychosis patients: a ten year longitudinal follow-up study. Schizophr. Res. 136 (1-3), 19–24.

Farkas, M., Polgar, P., Kelemen, O., Rethelyi, J., Bitter, I., Myers, C.E., Gluck, M.A., Keri, S., 2008. Associative learning in deficit and nondeficit schizophrenia. Neuroreport 19 (1), 55–58.

Fenton, W.S., McGlashan, T.H., 1994. Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. Am. J. Psychiatry 151 (3), 351–356.

Fenton, W.S., Wyatt, R.J., McGlashan, T.H., 1994. Risk factors for spontaneous dyskinesia in schizophrenia. Arch. Gen. Psychiatry 51 (8), 643–650.

Fervaha, G., Foussias, G., Agid, O., Remington, G., 2013. Amotivation and functional outcomes in early schizophrenia. Psychiatry Res. 210 (2), 665–668.

Fervaha, G., Agid, O., Foussias, G., Siddiqui, I., Takeuchi, H., Remington, G., 2015a. Neurocognitive impairment in the deficit subtype of schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci.

Fervaha, G., Duncan, M., Foussias, G., Agid, O., Faulkner, G.E., Remington, G., 2015b. Effort-based decision making as an objective paradigm for the assessment of motivational deficits in schizophrenia. Schizophr. Res. 168 (1-2), 483–490.

Fisher, D.J., Labelle, A., Knott, V.J., 2012. Alterations of mismatch negativity (MMN) in schizophrenia patients with auditory hallucinations experiencing acute exacerbation of illness. Schizophr. Res. 139 (1-3), 237–245.

Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. NeuroImage 62 (4), 2296–2314.

Foussias, G., Remington, G., 2010. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr. Bull. 36 (2), 359–369.

Foussias, G., Agid, O., Fervaha, G., Remington, G., 2014. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. Eur. Neuropsychopharmacol. 24 (5), 693–709.

Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., McGuire, P., 2015. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizophr. Bull. 41 (4), 892–899.

Galderisi, S., Maj, M., 2009. Deficit schizophrenia: an overview of clinical, biological and treatment aspects. Eur. Psychiatry 24 (8), 493–500.

Galderisi, S., Maj, M., Mucci, A., Cassano, G.B., Invernizzi, G., Rossi, A., Vita, A., Dell'Osso, L., Daneluzzo, E., Pini, S., 2002. Historical, psychopathological, neurological, and neuropsychological aspects of deficit schizophrenia: a multicenter study. Am. J. Psychiatry 159 (6), 983–990.

Galderisi, S., Quarantelli, M., Volpe, U., Mucci, A., Cassano, G.B., Invernizzi, G., Rossi, A., Vita, A., Pini, S., Cassano, P., Daneluzzo, E., De Peri, L., Stratta, P., Brunetti, A., Maj, M., 2008. Patterns of structural MRI abnormalities in deficit and nondeficit schizophrenia. Schizophr. Bull. 34 (2), 393–401.

Galderisi, S., Bucci, P., Mucci, A., Kirkpatrick, B., Pini, S., Rossi, A., Vita, A., Maj, M., 2013a. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. Schizophr. Res. 147 (1), 157–162.

Galderisi, S., Mucci, A., Bitter, I., Libiger, J., Bucci, P., Fleischhacker, W.W., Kahn, R.S., Eufest Study Group, 2013b. Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. Eur. Neuropsychopharmacol. 22, 196–204.

Galderisi, S., Rossi, A., Rocca, P., Bertolino, A., Mucci, A., Bucci, P., Rucci, P., Gibertoni, D., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Brugnoli, R., Dell'Osso, L., De Ronchi, D., Di Emidio, G., Di Giannantonio, M., Fagiolini, A., Marchesi, C., Monteleone, P., Oldani, L., Pinna, F., Roncone, R., Sacchetti, E., Santonastaso, P., Siracusano, A., Vita, A., Zeppegno, P., Maj, M., 2014. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry 13 (3), 275–287.

Gallagher, B.J., Jones, B.J., McFalls Jr., J.A., Pisa, A.M., 2007. Schizophrenic subtype, seasonality of birth and social class: a preliminary analysis. Eur. Psychiatry 22 (2), 123–128.

Gerbaldo, H., Georgi, K., Pieschl, D., 1997. The deficit syndrome in first-admission patients with psychotic and non-psychotic disorders. Eur. Psychiatry 12 (2), 53–57.

Goetz, R.R., Corcoran, C., Yale, S., Stanford, A.D., Kimhy, D., Amador, X., Malaspina, D., 2007. Validity of a 'proxy' for the deficit syndrome derived from the Positive And Negative Syndrome Scale (PANSS). Schizophr. Res. 93 (1-3), 169–177.

Goff, D.C., Tsai, G., Manoach, D.S., Coyle, J.T., 1995. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. Am. J. Psychiatry 152 (8), 1213–1215.

Goff, D.C., Tsai, G., Levitt, J., Amico, E., Manoach, D., Schoenfeld, D.A., Hayden, D.L., McCarley, R., Coyle, J.T., 1999. A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch. Gen. Psychiatry 56 (1), 21–27.

Goff, D.C., Bottiglieri, T., Arning, E., Shih, V., Freudenreich, O., Evins, A.E., Henderson, D.C., Baer, L., Coyle, J., 2004. Folate, homocysteine, and negative symptoms in schizophrenia. Am. J. Psychiatry 161 (9), 1705–1708.

Gonul, A.S., Kula, M., Esel, E., Tutus, A., Sofuoglu, S., 2003. A Tc-99m HMPAO SPECT study of regional cerebral blood flow in drug-free schizophrenic patients with deficit and non-deficit syndrome. Psychiatry Res. 123 (3), 199–205.

Gonzalez-Valderrama, A., Castaneda, C.P., Mena, C., Undurraga, J., Mondaca, P., Yanez, M., Bedregal, P., Nachar, R., 2015. Duration of untreated psychosis and acute remission of negative symptoms in a South American first-episode psychosis cohort. Early Interv. Psychiatry.

Gorissen, M., Sanz, J.C., Schmand, B., 2005. Effort and cognition in schizophrenia patients. Schizophr. Res. 78 (2-3), 199–208.

Hartmann, M.N., Hager, O.M., Reimann, A.V., Chumbley, J.R., Kirschner, M., Seifritz, E., Tobler, P.N., Kaiser, S., 2015. Apathy but not diminished expression in schizophrenia

is associated with discounting of monetary rewards by physical effort. Schizophr. Bull. 41, 503–512.
Harvey, P.D., Koren, D., Reichenberg, A., Bowie, C.R., 2006. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr. Bull. 32 (2), 250–258.
Heckers, S., Goff, D., Schacter, D.L., Savage, C.R., Fischman, A.J., Alpert, N.M., Rauch, S.L., 1999. Functional imaging of memory retrieval in deficit vs nondeficit schizophrenia. Arch. Gen. Psychiatry 56 (12), 1117–1123.
Heresco-Levy, U., Javitt, D.C., Ermilov, M., Mordel, C., Silipo, G., Lichtenstein, M., 1999. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch. Gen. Psychiatry 56 (1), 29–36.
Hong, L.E., Avila, M.T., Adami, H., Elliot, A., Thaker, G.K., 2003. Components of the smooth pursuit function in deficit and nondeficit schizophrenia. Schizophr. Res. 63 (1-2), 39–48.
Horga, G., Cassidy, C.M., Xu, X., Moore, H., Slifstein, M., Van Snellenberg, J.X., Abi-Dargham, A., 2016. Dopamine-related disruption of functional topography of striatal connections in unmedicated patients with schizophrenia. JAMA Psychiatry.
Hovington, C.L., Lepage, M., 2012. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. Expert. Rev. Neurother. 12 (1), 53–69.
Hovington, C.L., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2012. Identifying persistent negative symptoms in first episode psychosis. BMC Psychiatry 12, 224.
Hovington, C.L., Bodnar, M., Joober, R., Malla, A.K., Lepage, M., 2013. Impairment in verbal memory observed in first episode psychosis patients with persistent negative symptoms. Schizophr. Res. 147 (2-3), 223–229.
Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III–the final common pathway. Schizophr. Bull. 35 (3), 549–562.
Kallel, L., Brunelin, J., Zghal, A., Labbane, R., Dalery, J., d'Amato, T., Saoud, M., 2007. Summer birth and deficit schizophrenia in Tunisia. Psychiatry Res. 152 (2-3), 273–275.
Kinon, B.J., Noordsy, D.L., Liu-Seifert, H., Gulliver, A.H., Ascher-Svanum, H., Kollack-Walker, S., 2006. Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. J. Clin. Psychopharmacol. 26 (5), 453–461.
Kirkpatrick, B., 2014. Recognizing primary vs secondary negative symptoms and apathy vs expression domains. J. Clin. Psychiatry 75 (4), e09.
Kirkpatrick, B., Galderisi, S., 2008. Deficit schizophrenia: an update. World Psychiatry 7 (3), 143–147.
Kirkpatrick, B., Buchanan, R.W., McKenney, P.D., Alphs, L.D., Carpenter Jr., W.T., 1989. The schedule for the deficit syndrome: an instrument for research in schizophrenia. Psychiatry Res. 30, 119–123.
Kirkpatrick, B., Buchanan, R.W., Breier, A., Carpenter Jr., W.T., 1993. Case identification and stability of the deficit syndrome of schizophrenia. Psychiatry Res. 47 (1), 47–56.
Kirkpatrick, B., Buchanan, R.W., Breier, A., Carpenter Jr., W.T., 1994. Depressive symptoms and the deficit syndrome of schizophrenia. J. Nerv. Ment. Dis. 182 (8), 452–455.
Kirkpatrick, B., Ram, R., Bromet, E., 1996a. The deficit syndrome in the Suffolk County Mental Health Project. Schizophr. Res. 22 (2), 119–126.
Kirkpatrick, B., Amador, X.F., Flaum, M., Yale, S.A., Gorman, J.M., Carpenter Jr., W.T., Tohen, M., McGlashan, T., 1996b. The deficit syndrome in the DSM-IV Field Trial: I. Alcohol and other drug abuse. Schizophr. Res. 20 (1-2), 69–77.
Kirkpatrick, B., Ram, R., Amador, X.F., Buchanan, R.W., McGlashan, T., Tohen, M., Bromet, E., 1998. Summer birth and the deficit syndrome of schizophrenia. Am. J. Psychiatry 155 (9), 1221–1226.
Kirkpatrick, B., Castle, D., Murray, R.M., Carpenter Jr., W.T., 2000. Risk factors for the deficit syndrome of schizophrenia. Schizophr. Bull. 26 (1), 233–242.
Kirkpatrick, B., Buchanan, R.W., Ross, D.E., Carpenter Jr., W.T., 2001. A separate disease within the syndrome of schizophrenia. Arch. Gen. Psychiatry 58 (2), 165–171.
Kirkpatrick, B., Tek, C., Allardyce, J., Morrison, G., McCreadie, R.G., 2002. Summer birth and deficit schizophrenia in Dumfries and Galloway, southwestern Scotland. Am. J. Psychiatry 159 (8), 1382–1387.
Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32 (2), 214–219.
Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Danie, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. Schizophr. Bull. 37 (2), 300–305.
Kirschner, M., Hager, O.M., Bischof, M., Hartmann, M.N., Kluge, A., Seifritz, E., Tobler, P.N., Kaiser, S., 2016. Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. J. Psychiatry Neurosci. 41 (3), 152–161.
Kitis, O., Ozalay, O., Zengin, E.B., Haznedaroglu, D., Eker, M.C., Yalvac, D., Oguz, K., Coburn, K., Gonul, A.S., 2012. Reduced left uncinate fasciculus fractional anisotropy in deficit schizophrenia but not in non-deficit schizophrenia. Psychiatry Clin. Neurosci. 66 (1), 34–43.
Kopelowicz, A., Zarate, R., Tripodis, K., Gonzalez, V., Mintz, J., 2000. Differential efficacy of olanzapine for deficit and nondeficit negative symptoms in schizophrenia. Am. J. Psychiatry 157 (6), 987–993.
Kring, A.M., Gur, R.E., Blanchard, J.J., Horan, W.P., Reise, S.P., 2013. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am. J. Psychiatry 170 (2), 65–172.
Lahti, A.C., Holcomb, H.H., Medoff, D.R., Weiler, M.A., Tamminga, C.A., Carpenter Jr., W.T., 2001. Abnormal patterns of regional cerebral blood flow in schizophrenia with primary negative symptoms during an effortful auditory recognition task. Am. J. Psychiatry 158 (11), 1797–1808.
Larsen, T.K., Melle, I., Auestad, B., Haahr, U., Joa, I., Johannessen, J.O., Opjordsmoen, S., Rund, B.R., Rossberg, J.I., Simonsen, E., Vaglum, P., Friis, S., McGlashan, T., 2011. Early detection of psychosis: positive effects on 5-year outcome. Psychol. Med. 41 (7), 1461–1469.
Leucht, S., Pitschel-Walz, G., Engel, R.R., Kissling, W., 2002. Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am. J. Psychiatry 159 (2), 180–190.
Li, Z., Zheng, B., Deng, W., Liu, X., Zheng, Z., Li, T., 2013. Multi-components of evoked-brain potentials in deficit and nondeficit schizophrenia. Asia Pac. Psychiatry 5, 69–79.
Li, Z., Deng, W., Liu, X., Zheng, Z., Li, M., Li, Y., Han, Y., Ma, X., Wang, Q., Liu, X., Li, T., 2015. Contingent negative variation in patients with deficit schizophrenia or bipolar I disorder with psychotic features: measurement and correlation with clinical characteristics. Nord. J. Psychiatry 69 (3), 196–203.
Lindenmayer, J.P., Khan, A., Iskander, A., Abad, M.T., Parker, B., 2007. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. J. Clin. Psychiatry 68 (3), 368–379.
Lubeiro, A., Rueda, C., Hernández, J.A., Sanz, J., Sarramea, F., Molina, V., 2016. Identification of two clusters within schizophrenia with different structural, functional and clinical characteristics. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 64, 79–86.
Ludewig, K., Vollenweider, F.X., 2002. Impaired sensorimotor gating in schizophrenia with deficit and with nondeficit syndrome. Swiss Med. Wkly. 132 (13-14), 159–165.
Mäkinen, J., Miettunen, J., Isohanni, M., Koponen, H., 2008. Negative symptoms in schizophrenia: a review. Nord. J. Psychiatry 62 (5), 334–341.
Malaspina, D., Coleman, E., Goetz, R.R., Harkavy-Friedman, J., Corcoran, C., Amador, X., Yale, S., Gorman, J.M., 2002. Odor identification, eye tracking and deficit syndrome schizophrenia. Biol. Psychiatry 51 (10), 809–815.
Malla, A.K., Takhar, J.J., Norman, R.M., Manchanda, R., Cortese, L., Haricharan, R., Verdi, M., Ahmed, R., 2002. Negative symptoms in first episode non-affective psychosis. Acta Psychiatr. Scand. 105 (6), 431–439.
Malla, A.K., Norman, R.M., Takhar, J., Manchanda, R., Townsend, L., Scholten, D., Haricharan, R., 2004. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J. Nerv. Ment. Dis. 192, 455–463.
Marder, S.R., Kirkpatrick, B., 2014. Defining and measuring negative symptoms of schizophrenia in clinical trials. Eur. Neuropsychopharmacol. 24 (5), 737–743.
Marder, S.R., Daniel, D.G., Alphs, L., Awad, A.G., Keefe, R.S., 2011. Methodological issues in negative symptom trials. Schizophr. Bull. 37 (2), 250–254.
Mayerhoff, D.I., Loebel, A.D., Alvir, J.M., Szymanski, S.R., Geisler, S.H., Borenstein, M., Lieberman, J.A., 1994. The deficit state in first-episode schizophrenia. Am. J. Psychiatry 151 (10), 1417–1422.
Messias, E., Kirkpatrick, B., 2001. Summer birth and the deficit syndrome of schizophrenia in The Epidemiological Catchment Area study. J. Nerv. Ment. Dis. 189, 608–612.
Messias, E., Kirkpatrick, B., Bromet, E., Ross, D., Buchanan, R.W., Carpenter Jr., W.T., Tek, C., Kendler, K.S., Walsh, D., Dollfus, S., 2004. Summer birth and deficit schizophrenia: a pooled analysis from 6 countries. Arch. Gen. Psychiatry 61 (10), 985–989.
Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am. J. Psychiatry 162, 495–506.
Miller, E.M., Shankar, M.U., Knutson, B., McClure, S.M., 2014. Dissociating motivation from reward in human striatal activity. J. Cogn. Neurosci. 26 (5), 1075–1084.
Möller, H.J., Riedel, M., Müller, N., Fischer, W., Kohnen, R., 2004. Zotepine versus placebo in the treatment of schizophrenic patients with stable primary negative symptoms: a randomized double-blind multicenter trial. Pharmacopsychiatry 37 (6), 270–278.
Morra, L.F., Gold, J.M., Sullivan, S.K., Strauss, G.P., 2015. Predictors of neuropsychological effort test performance in schizophrenia. Schizophr. Res. 162 (1-3), 205–210.
Morris, R.W., Quail, S., Griffiths, K.R., Green, M.J., Balleine, B.W., 2015. Corticostriatal control of goal-directed action is impaired in schizophrenia. Biol. Psychiatry 77 (2), 187–195.
Mucci, A., Galderisi, S., Kirkpatrick, B., Bucci, P., Volpe, U., Merlotti, E., Centanaro, F., Catapano, F., Maj, M., 2007. Double dissociation of N1 and P3 abnormalities in deficit and nondeficit schizophrenia. Schizophr. Res. 92 (1-3), 252–261.
Mucci, A., Dima, D., Soricelli, A., Volpe, U., Bucci, P., Frangou, S., Prinster, A., Salvatore, M., Galderisi, S., Maj, M., 2015a. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. Psychol. Med. 45 (8), 1765–1778.
Mucci, A., Galderisi, S., Merlotti, E., Rossi, A., Rocca, P., Bucci, P., Piegari, G., Chieffi, M., Vignapiano, A., Maj, M., Italian Network for Research on Psychoses, 2015b. The Brief Negative Symptom Scale (BNSS): independent validation in a large sample of Italian patients with schizophrenia. Eur. Psychiatry 30 (5), 641–647.
Murphy, B.P., Chung, Y.C., Park, T.W., McGorry, P.D., 2006. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr. Res. 88 (1-3), 5–25.
Nkam, I., Thibaut, F., Denise, P., Van Der Elst, A., Segard, L., Brazo, P., Menard, J., Thery, S., Halbeck, I., Delamilleure, P., Vasse, T., Etard, O., Dollfus, S., Champion, D., Levillain, D., Petit, M., 2001. Saccadic and smooth-pursuit eye movements in deficit and non-deficit schizophrenia. Schizophr. Res. 48 (1), 145–153.
Nkam, I., Bocca, M.L., Denise, P., Paoletti, X., Dollfus, S., Levillain, D., Thibaut, F., 2010. Impaired smooth pursuit in schizophrenia results from prediction impairment only. Biol. Psychiatry 67 (10), 992–997.
Olie, J.P., Spina, E., Murray, S., Yang, R., 2006. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. Int. Clin. Psychopharmacol. 21 (3), 143–151.
Palmiter, R.D., 2008. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice. Ann. N. Y. Acad. Sci. 1129, 35–46.
Peralta, V., Cuesta, M.J., 2004. The deficit syndrome of the psychotic illness. A clinical and nosological study. Eur. Arch. Psychiatry Clin. Neurosci. 254 (3), 165–171.
Peralta, V., Moreno-Izco, L., Sanchez-Torres, A., García de Jalón, E., Campos, M.S., Cuesta, M.J., 2014. Characterization of the deficit syndrome in drug-naive schizophrenia patients: the role of spontaneous movement disorders and neurological soft signs. Schizophr. Bull. 40 (1), 214–224.
Polgár, P., Farkas, M., Nagy, O., Kelemen, O., Réthelyi, J., Bitter, I., Myers, C.E., Gluck, M.A., Kéri, S., 2008. How to find the way out from four rooms? The learning of "chaining" associations may shed light on the neuropsychology of the deficit syndrome of schizophrenia. Schizophr. Res. 99 (1-3), 200–207.

Polgár, P., Réthelyi, J.M., Balint, S., Komlosi, S., Czobor, P., Bitter, I., 2010. Executive function in deficit schizophrenia: what do the dimensions of the Wisconsin Card Sorting Test tell us? Schizophr. Res. 122 (1-3), 85–93.
Quarantelli, M., Larobina, M., Volpe, U., Amati, G., Tedeschi, E., Ciarmiello, A., Brunetti, A., Galderisi, S., Alfano, B., 2002. Stereotaxy-based regional brain volumetry applied to segmented MRI: validation and results in deficit and nondeficit schizophrenia. NeuroImage 17 (1), 373–384.
Rabinowitz, J., Werbeloff, N., Caers, I., Mandel, F.S., Stauffer, V., Menard, F., Kinon, B.J., Kapur, S., 2013. Negative symptoms in schizophrenia–the remarkable impact of inclusion definitions in clinical trials and their consequences. Schizophr. Res. 150 (2-3), 334–338.
Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., Fusar-Poli, P., 2015. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis. JAMA Psychiatry 72 (12), 1243–1251.
Réthelyi, J.M., Czobor, P., Polgar, P., Mersich, B., Balint, S., Jekkel, E., Magyar, K., Meszaros, A., Fabian, A., Bitter, I., 2012. General and domain-specific neurocognitive impairments in deficit and non-deficit schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 262 (2), 107–115.
Riedel, M., Muller, N., Strassnig, M., Spellmann, I., Engel, R.R., Musil, R., Dehning, S., Douhet, A., Schwarz, M.J., Moller, H.J., 2005. Quetiapine has equivalent efficacy and superior tolerability to risperidone in the treatment of schizophrenia with predominantly negative symptoms. Eur. Arch. Psychiatry Clin. Neurosci. 255 (6), 432–437.
Rosenheck, R., Evans, D., Herz, L., Cramer, J., Xu, W., Thomas, J., Henderson, W., Charney, D., 1999. How long to wait for a response to clozapine: a comparison of time course of response to clozapine and conventional antipsychotic medication in refractory schizophrenia. Schizophr. Bull. 25 (4), 709–719.
Ross, D.E., Thaker, G.K., Buchanan, R.W., Lahti, A.C., Medoff, D., Bartko, J.J., Moran, M., Hartley, J., 1996. Association of abnormal smooth pursuit eye movements with the deficit syndrome in schizophrenic patients. Am. J. Psychiatry 153 (9), 1158–1165.
Ross, D.E., Thaker, G.K., Buchanan, R.W., Kirkpatrick, B., Lahti, A.C., Medoff, D., Bartko, J.J., Goodman, J., Tien, A., 1997. Eye tracking disorder in schizophrenia is characterized by specific ocular motor defects and is associated with the deficit syndrome. Biol. Psychiatry 42 (9), 781–796.
Ross, D.E., Buchanan, R.W., Medoff, D., Lahti, A.C., Thaker, G.K., 1998. Association between eye tracking disorder in schizophrenia and poor sensory integration. Am. J. Psychiatry 155 (10), 1352–1357.
Ross, D.E., Kirkpatrick, B., Karkowski, L.M., Straub, R.E., MacLean, C.J., O'Neill, F.A., Compton, A.D., Murphy, B., Walsh, D., Kendler, K.S., 2000. Sibling correlation of deficit syndrome in the Irish study of high-density schizophrenia families. Am. J. Psychiatry 157 (7), 1071–1076.
Rowland, L.M., Spieker, E.A., Francis, A., Barker, P.B., Carpenter, W.T., Buchanan, R.W., 2009. White matter alterations in deficit schizophrenia. Neuropsychopharmacology 34 (6), 1514–1522.
Roy, M.A., Mérette, C., Maziade, M., 2001a. Subtyping schizophrenia according to outcome or severity: a search for homogeneous subgroups. Schizophr. Bull. 27 (1), 115–138.
Roy, M.A., Maziade, M., Labbé, A., Mérette, C., 2001b. Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr. Res. 47 (2-3), 141–147.
Santos, J.L., Sánchez-Morla, E.M., Aparicio, A., García-Jiménez, M.A., Villanueva, C., Martínez-Vizcaíno, V., Arango, C., 2010. P50 gating in deficit and nondeficit schizophrenia. Schizophr. Res. 119 (1-3), 183–190.
Skudlarski, P., Jagannathan, K., Anderson, K., Stevens, M.C., Calhoun, V.D., Skudlarska, B.A., Pearlson, G., 2010. Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. Biol. Psychiatry 68 (1), 61–69.
Spalletta, G., De Rossi, P., Piras, F., Iorio, M., Dacquino, C., Scanu, F., Girardi, P., Caltagirone, C., Kirkpatrick, B., Chiapponi, C., 2015. Brain white matter microstructure in deficit and non-deficit subtypes of schizophrenia. Psychiatry Res. 231 (3), 252–261.
Stauffer, V.L., Song, G., Kinon, B.J., Ascher-Svanum, H., Chen, L., Feldman, P.D., Conley, R.R., 2012. Responses to antipsychotic therapy among patients with schizophrenia or schizoaffective disorder and either predominant or prominent negative symptoms. Schizophr. Res. 134 (2-3), 195–201.
Strauss, G.P., Harrow, M., Grossman, L.S., Rosen, C., 2010. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. Schizophr. Bull. 36 (4), 788–799.
Strauss, G.P., Morra, L.F., Sullivan, S.K., Gold, J.M., 2015. The role of low cognitive effort and negative symptoms in neuropsychological impairment in schizophrenia. Neuropsychology 29 (2), 282–291.
Subotnik, K.L., Nuechterlein, K.H., Ventura, J., Green, M.F., Hwang, S.S., 1998a. Prediction of the deficit syndrome from initial deficit symptoms in the early course of schizophrenia. Psychiatry Res. 80 (1), 53–59.
Subotnik, K.L., Nuechterlein, K.H., Ventura, J., 2000. MMPI discriminators of deficit vs. nondeficit recent-onset schizophrenia patients. Psychiatry Res. 93 (2), 111–123.
Tamminga, C.A., Thaker, G.K., Buchanan, R., Kirkpatrick, B., Alphs, L.D., Chase, T.N., Carpenter, W.T., 1992. Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. Arch. Gen. Psychiatry 49 (7), 522–530.
Tek, C., Kirkpatrick, B., Buchanan, R.W., 2001. A five-year follow up study of deficit and nondeficit schizophrenia. Schizophr. Res. 49 (3), 253–260.
Telfer, S., Shivashankar, S., Krishnadas, R., McCreadie, R.G., Kirkpatrick, B., 2011. Tardive dyskinesia and deficit schizophrenia. Acta Psychiatr. Scand. 124 (5), 357–362.
Ten Velden Hegelstad, W., Haahr, U., Larsen, T.K., Auestad, B., Barder, H., Evensen, J., Joa, I., Johannessen, J.O., Langeveld, J., Melle, I., Opjordsmoen, S., Rossberg, J.I., Rund, B.R., Simonsen, E., Vaglum, P., McGlashan, T., Friis, S., 2013. Early detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study. Schizophr. Res. 143 (2-3), 337–343.
Tiryaki, A., Yazici, M.K., Anil, A.E., Kabakçi, E., Karaağaoğlu, E., Göğüş, A., 2003. Reexamination of the characteristics of the deficit schizophrenia patients. Eur. Arch. Psychiatry Clin. Neurosci. 253 (5), 221–227.
Turetsky, B., Cowell, P.E., Gur, R.C., Grossman, R.I., Shtasel, D.L., Gur, R.E., 1995. Frontal and temporal lobe brain volumes in schizophrenia. Relationship to symptoms and clinical subtype. Arch. Gen. Psychiatry 52, 1061–1070.
Turetsky, B.I., Colbath, E.A., Gur, R.E., 1998. P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. Biol. Psychiatry 43 (2), 84–96.
Üçok, A., Ergül, C., 2014. Persistent negative symptoms after first episode schizophrenia: a 2-year follow-up study. Schizophr. Res. 158 (1-3), 241–246.
Vaiva, G., Cottencin, O., Llorca, P.M., Devos, P., Dupont, S., Mazas, O., Rascle, C., Thomas, P., Steinling, M., Goudemand, M., 2002. Regional cerebral blood flow in deficit/nondeficit types of schizophrenia according to SDS criteria. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 26 (3), 481–485.
Ventura, K.L., Gitlin, M.J., Gretchen-Doorly, D., Ered, A., Villa, K.F., Hellemann, G.S., Nuechterlein, K.H., 2015. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. Schizophr. Res. 161 (2-3), 407–413.
Vogel, S.J., Strauss, G.P., Allen, D.N., 2013. Using negative feedback to guide behavior: impairments on the first 4 cards of the Wisconsin Card Sorting Test predict negative symptoms of schizophrenia. Schizophr. Res. 151 (1-3), 97–101.
Voineskos, A.N., Foussias, G., Lerch, J., Felsky, D., Remington, G., Rajji, T.K., Lobaugh, N., Pollock, B.G., Mulsant, B.H., 2013. Neuroimaging evidence for the deficit subtype of schizophrenia. JAMA Psychiatry 70 (5), 472–480.
Volpe, U., Mucci, A., Quarantelli, M., Galderisi, S., Maj, M., 2012. Dorsolateral prefrontal cortex volume in patients with deficit or nondeficit schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 37 (2), 264–269.
Wang, X., Yao, S., Kirkpatrick, B., Shi, C., Yi, J., 2008. Psychopathology and neuropsychological impairments in deficit and nondeficit schizophrenia of Chinese origin. Psychiatry Res. 158 (2), 195–205.
Wheeler, A.L., Wessa, M., Szeszko, P.R., Foussias, G., Chakravarty, M.M., Lerch, J.P., DeRosse, P., Remington, G., Mulsant, B.H., Linke, J., Malhotra, A.K., Voineskos, A.N., 2015. Further neuroimaging evidence for the deficit subtype of schizophrenia: a cortical connectomics analysis. JAMA Psychiatry 72 (5), 446–455.
Yu, M., Tang, X., Wang, X., Zhang, X., Zhang, X., Sha, W., Yao, S., Shu, N., Zhang, X., Zhang, Z., 2015. Neurocognitive impairments in deficit and non-deficit schizophrenia and their relationships with symptom dimensions and other clinical variables. PLoS One 10 (9), e0138357.
Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr. Res. 67 (2-3), 131–142.
Zalesky, A., Fornito, A., Seal, M.L., Cocchi, L., Westin, C.F., Bullmore, E.T., Egan, G.F., Pantelis, C., 2011. Disrupted axonal fiber connectivity in schizophrenia. Biol. Psychiatry 69 (1), 80–89.