Although NS were considered fundamental by Bleuler, the DSM classifications favoured the Schneiderian symptoms because these are easier to identify, to assess and responded to classical neuroleptics. T. Crow stimulated research in this area by proposing that NS reflected a different etiopathogenic process not responsive to treatment. In parallel, different multidimensional analysis of symptomatology progressively defined the core symptoms of this dimension and the importance of environmental factors (neuroleptics, improvement of positive symptoms, institutionalisation) was underlined leading to the concept of primary and secondary negative symptoms. Different epidemiological findings suggest that NS are central in schizophrenia:

- Their presence is correlated with the presence of neurological soft signs.
- Twin studies show a better concordance of NS in monozygotic twins not found for positive symptoms.
- Positive symptoms fluctuate during evolution while NS remain stable, specially anhedonia, affective blunting, avolition. The same symptoms appear to be linked to a poor outcome in most studies with a duration >2 years. When the early stage of schizophrenia and premorbid symptomatology is considered again NS appear to be the most common early signs. During the premorbid phase, NS (withdrawal, anhedonia, restricted interest) are characteristic together with unusual thoughts and abstraction and learning difficulties. In addition, these early premorbid signs are related to the stable negative symptomatology during the active phase of the illness. Therefore, not only NS at the origin of the long term burden induced by schizophrenia but they appear to be the most constant phenomenon from premorbid to the late stage of illness.

  Consequences of this finding will be discussed.

S12-2
NEGATIVE SYMPTOMS: CONCEPTS AND PATHOPHYSIOLOGY

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Negative symptoms reflect a diminished amount of mental activity, and include poverty of speech, affect and spontaneous movement. Some authors include a wider range of phenomena. For example, Andreasen also includes poor performance in occupational and social roles, and attentional impairment. However, it is likely that the broader definition of negative symptoms embraces features that reflect either reduced or disorganised mental activity. Even if we focus only on those symptoms that reflect reduced mental activity, several different pathophysiological processes contribute to these symptoms. The negative symptoms arising during an acute episode of illness tend to respond to antipsychotic medication, but those developing in the chronic phase are usually persistent, suggesting that different mechanisms are involved. PET studies indicate that negative symptoms are associated with evidence of frontal lobe underactivity. In severe, persistent cases, there is also evidence of reduced frontal grey matter. However, even in persistent cases, the frontal lobes are capable of activation under some circumstances. The pharmacological mechanisms involved in negative symptoms remain uncertain, though some evidence implicates dopaminergic underactivity.

S12-3
THE MEASUREMENT OF NEGATIVE SYMPTOMS

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All the scales used to evaluate negative symptoms such as SANS (Scale for the Assessment of Negative Symptoms, Andreasen), PANSS (Positive and Negative Syndrome Scale, Kay) do not distinguish primary from secondary negative symptoms and do not evaluate enduring negative symptoms. The measurement of the negative symptoms with these scales shows that negative symptoms are not necessarily stable during the course of illness and can vary with other symptoms (extrapyramidal, depression or positive symptoms). Indeed, in a longitudinal study, we showed that some negative symptoms improved with the decrease of akinesia and depression scores during the recovery of an acute phase while other negative symptoms such as unchanging facial expression, decreased spontaneous movements, paucity of expressive gestures, lack of vocal inflections and poverty of speech did not vary.

In order to measure primary and enduring symptoms, the Schedule of Deficit Syndrome (SDS, Kirkpatrick et al, 1989) can be used to categorize patients into deficit and non deficit subtypes.

In a large cohort of schizophrenic patients, we showed that the negative subtype defined with PANSS was not equivalent to the deficit subtype defined with SDS. Moreover, the Wisconsin Card Sorting Test (categorical and perseverative errors) was more impaired, antisaccades (rate and latency) and neurological abnormalities (soft signs) were significantly more frequent in deficit patients than in non deficit patients while no difference was observed between negative and non negative patients.

These results suggest that a cerebral dysfunction in particular in dorsolateral prefrontal cortex could be observed in deficit patients but not in all the negative patients in whom secondary negative symptoms can be observed.

S12-4
TREATMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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There is a strong debate in the literature whether neuroleptics are able to reduce negative symptoms and whether this is a direct or an indirect effect (e.g. via reduction of positive symptoms or via a better extrapyramidal tolerability). Nearly all trials on older neuroleptics are not designed to answer this question in a conclusive way. After a careful review of published studies on older neuroleptics in the treatment of negative symptoms, a final conclusion could not be drawn as to whether certain older neuroleptics are superior to other older neuroleptics with respect to negative symptoms or whether older neuroleptics in general are effective in primary negative symptoms. However, there is some evidence in negative symptoms accompanying positive symptoms to improve under the treatment with all neuroleptics, corresponding with amelioration of positive symptoms. Clozapine general seen as a first atypical antipsychotic seems to give some more evidence for a better effect on negative symptoms compared to older neuroleptics. However, also the Clozapine studies are generally lacking an advanced methodological standard concerning the evaluation of treatment effects on negative symptoms.

One of the primary goals in the development of new antipsychotics is efficacy in negative symptoms. Some of the new compounds brought on the market in the last years, like Risperidone,