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EDITORIAL

The emergence of primary negative symptoms: relevance of timing?

Eric Yu Hai Chen, Stephanie Ming Yin Wong, Christy Lai Ming Hui, Yi Nam Suen and Sherry Kit Wa Chan

Negative symptoms are an important symptom dimension in schizophrenia that are often least responsive to antipsychotic medications. We revisit the current practice of identifying 'primary' negative symptoms and suggest that its concept would benefit from a further elaboration of their timing of emergence in relation to the dynamic neurobiological changes to enhance their utility in clinical decision-making and research.

Keywords
Negative symptoms; primary negative symptoms; clinical decisions; psychopathology.

Negative symptoms (NS) have been recognised as an important group of features in schizophrenia. The concept of 'negativity' had been adopted in a Jacksonian sense, referring to the pathological loss of normal functions. Recent studies suggest that NS comprise two main groups: blunted affect and diminished motivation. While these symptoms have typically been associated with the diagnostic category of schizophrenia, recent studies that emphasise a more dimensional approach have also recognised the possible presentation of NS in other diagnostic categories of psychotic disorders, such as delusional disorder.[1]

It is well-recognised that NS in schizophrenia are associated with considerable cognitive dysfunctions and functional impairments. Compared to other aspects of schizophrenia, antipsychotic medications have not been very effective in ameliorating NS. Distinguishing between 'primary' and 'secondary' NS has hence generally been seen as an important task for guiding treatment options. 'Secondary' NSrefer to states in which the presence of NS is attributable to other identifiable causes, such as depressive mood and side effects of antipsychotic medication. Wolpe et al. (this issue) demonstrated that in addition to conventional antipsychotics, clozapine treatment can significantly increase NS – specifically the motivation and pleasure dimension – via its sedative side-effects. 'Primary' negative symptoms (PrNS), on the other hand, refer to features which are not attributable to these causes; rather, PrNS are considered to reflect a putative underlying 'deficit state' presumed to be linked to irreversible brain changes. In current practice, clinicians are encouraged to first screen for secondary NS – to rule out factors that may contribute to secondary NS – and ameliorate these symptoms. The recalcitrant NS are then typically considered to be 'primary,' 'persistent,' 'dominant', or a 'deficit state.' We suggest that the concept of 'primary negative symptoms' (PrNS) may benefit from further elaboration to enhance its usefulness in clinical practice and research.

The current concept of PrNS involves a process of 'diagnosis by exclusion,' which is not uncommon in psychiatry (e.g., the concept of *functional psychosis*). This approach presumes there exist some distinctive 'identifiable' causes (such as depression or antipsychotic side-effects) that can result in clinical phenomena of NS. If the phenomena are not due to identifiable causes, they are naturally attributed to a primary deficit associated with a presumably more intractable neurobiological mechanism. Underlying these is the assumption that these neurobiological changes are irreversible. Such an assumption has nonetheless been challenged by a growing number of recent observations, thereby reinforcing the view that even for patients with a chronic course of illness, some neurobiological changes may still be reversible.[2]

While the exact pathophysiology of NS has yet to be fully elucidated, studies have observed a range of neurobiological changes associated with PrNS, some of which have in fact been observed in conditions, such as depression, that may underlie secondary negative symptoms (e.g., reduced grey matter volume and task activation of the prefrontal cortex.[3] The sharing of at least some neurobiological changes between primary and secondary NS suggests that it may be premature to separate these two concepts as fundamentally distinct entities. Indeed, other instances of 'diagnosis by exclusion' throughout history remind us that from time to time, new discoveries would slice off a section of a 'primary' disorder and relocate it within the 'secondary' domain (e.g., general paralysis of the insane, or NMDA-receptor autoantibodies psychosis).

This awareness provides crucial context for our consideration of an important observation in schizophrenia-spectrum disorders: that levels of NS can vary across phases and the course of the conditions. Features of NS have been identified in earlier phases of the condition, including in high-risk states and first-episode psychosis (as observed in Salazar de Pablo et al, this issue); they may also evolve during the initial years of the disorder and may undergo further changes in subsequent phases. While some may argue that if they had changed at all, they should not be considered as 'primary'. This perspective, nevertheless, fails to recognise the possibility that the neurobiological process underlying the key features of NS could also evolve dynamically as a result of life-course brain changes in relation to development and ageing.

As such, the *timing* of the emergence of PrNS can provide important information concerning the longitudinal evolution of psychotic disorders. While the field of psychosis has moved away from a simplistic 'neurodevelopmental-only' paradigm, the current understanding of additional processes implicated in the expression of the disorder remains limited. Unlike positive symptoms, obtaining information about the time course of NS in an individual, particularly PrNS, can nevertheless be extremely challenging. It is recognised that there may be reductions in grey matter brain volume with time, which could potentially be associated with the later emergence of NS. In this context, the timing of changes in the levels of PrNS may signal the unfolding of neurobiological processes over the course of the disorder. Recognition and the charting of PrNS and their related processes may offer new insights and facilitate further explorations of therapeutic possibilities.

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The timing of the onset and proliferation of NS is also largely relevant to the consideration of whether such changes could relate to factors such as genetics, early brain neurodevelopment, maturational synaptic pruning, responses to trauma, substance use, prodromal brain state changes, untreated psychosis, or those relating to the resolving of psychosis. Salazar de Pablo et al. (this issue) showed that NS are present in early onset psychosis as well as clinical high risk states, and are associated with poor outcome. At the same time, it is also important to characterise the relationship of NS with relapse, treatment resistance, ageing, and environmental interactions during the course of illness over extended time frames. For example, Wolpe et at (this issue) observe that NS could be associated with clozapine treatment.

While some perspectives emphasise the presence of poor premorbid adjustment in the definition of PrNS,[4] from a life course perspective, we propose that PrNS that arise after illness onset should also be included. In fact, they should be further considered in relation to their putative neurobiological origins. For example, PrNS that emerged during childhood and early adolescence may be mostly attributable to the genetics of early brain development processes, while PrNS that emerged only during adolescence as a new phenomenon (but were absent before this period) may be more closely linked to processes related to the adolescent brain development, such as synaptic pruning. PrNS that arise closer to the onset of the psychotic disorder may be related to the unique brain changes in relation to the first psychotic episode. In addition, it should be recognised that PrNS could emerge upon the remission of psychotic symptoms that are unrelated to either medication or depressed mood.[1] Studies have indeed observed the emergence of PrNS as late as three to four years after the first-episode illness.[5] Furthermore, with the active evolution of neurobiological processes during these later stages (such as brain volume change), the possible interactions between the psychotic disorder and ageing-related degenerative brain processes (such as Parkinson's disease) may also play a role in the pathogenesis of late PrNS.

As a group of phenomena characterised by the blunting of affect and lack of motivation, the shared phenomenological expression of different negative features may mask the diversity of underlying aetiological factors. The timing of their emergence is potentially important in linking NS with stage-specific brain processes. In addition to the consideration of NS secondary to mood, extrapyramidal symptoms, and psychosis, we propose further subtyping of PrNS based on the stages of their emergence, for instance, into the following groups: early developmental NS, adolescent-emergent NS, risk-state-related NS, first-episode-related NS, mid-course NS, late NS.

In current clinical practice, NS, particularly PrNS, may not be systematically recorded in medical records. Disciplined longitudinal observations would be required to identify the emergence and evolution of PrNS. Careful documentation of the time course of NS should allow clinicians to pinpoint the emergence of PrNS and relate them to different brain development stages. Such considerations would facilitate more refined studies of the prevalence of primary and secondary NS, their putative aetiological factors, and associated clinical and neurobiological processes, and thereby improve our understanding of the conditions and guide treatment decisions.

Eric Yu Hai Chen, MA(Oxon), MBChB(Edin), MD(Edin), FRCPsych, FHKAM(Psychiatry), Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong; **Stephanie Ming Yin Wong**, Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong; **Christy Lai Ming Hui**, Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong; **Yi Nam Suen**, Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong; **Sherry Kit Wa Chan**, Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong

Correspondence: Eric Yu Hai Chen, Department of Psychiatry, The University of Hong Kong, Department of Psychiatry, 2/F New Clinical Building, Queen Mary Hospital, Pokfulam Road, Hong Kong. Email: eyhchen.hk@gmail.com

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