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Secondary negative symptoms — A review of mechanisms, assessment and treatment

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ABSTRACT

Negative symptoms in schizophrenia may be classified as primary or secondary. Primary negative symptoms are thought to be intrinsic to schizophrenia, while secondary negative symptoms are caused by positive symptoms, depression, medication side-effects, social deprivation or substance abuse. Most of the research on secondary negative symptoms has aimed at ruling them out in order to isolate primary negative symptoms. However, secondary negative symptoms are common and can have a major impact on patient-relevant outcomes. Therefore, the assessment and treatment of secondary negative symptoms are clinically relevant. Furthermore, understanding the mechanisms underlying secondary negative symptoms can contribute to an integrated model of negative symptoms. In this review we provide an overview of concepts, evidence, assessment and treatment for the major causes of secondary negative symptoms. We also summarize neuroimaging research relevant to secondary negative symptoms. We emphasize the relevance of recent developments in psychopathological assessment of negative symptoms, such as the distinction between amotivation and diminished expression, which have only rarely been applied in research on secondary negative symptoms.

1. Introduction

Negative symptoms are a core deficit in schizophrenia and can be considered to represent two dimensions (Blanchard and Cohen, 2006; Liemburg et al., 2013; Strauss et al., 2014). First, the motivational dimension, which we refer to as amotivation, combines anhedonia, avolition, and asociality. Second, the diminished expression dimension includes blunted affect and alogia. Negative symptoms contribute strongly to poor functional outcome and reduced quality of life (Milev et al., 2005; Strauss et al., 2010, 2013; Galderisi et al., 2013, 2014). An important causal distinction has been made between primary and secondary negative symptoms (Fig. 1). Primary negative symptoms are thought to be intrinsic to schizophrenia, while secondary negative symptoms are caused by positive symptoms, depression, medication side-effects, social deprivation and substance abuse (Carpenter et al., 1985; Kirkpatrick, 2014). Most research employing this distinction has focused on the definition of primary and persistent negative symptoms or deficit symptoms and has not focused on secondary negative symptoms as a primary outcome measure (Carpenter et al., 1988; Kirkpatrick et al., 1989). However, secondary negative symptoms have considerable clinical relevance for two reasons. First, secondary negative symptoms are more prevalent than primary negative symptoms and occur in more than half of patients with schizophrenia (Bobes et al., 2010; Lyne et al., 2015). Second, since secondary negative symptoms have often clearly defined causes, they should be easier to treat than primary ones.

At a clinical level both types of negative symptoms often appear to have similar or even identical phenomenology. Therefore, they are not easily distinguished with negative symptom scores without additional information about other symptom dimensions or environmental factors (Kirkpatrick, 2014). However, in clinical practice it is crucial to be aware of the mechanisms underlying secondary negative symptoms. Hence, our primary aim is to review the evidence and treatment options for each individual cause of secondary negative symptoms in schizophrenia.

In addition to the clinical relevance, it is important to elucidate the underlying pathophysiological mechanisms of secondary negative symptoms for two reasons. First, given the fact that both primary and secondary negative symptoms have strongly overlapping phenomenological properties one would expect some shared pathophysiology. Thus, the study of secondary negative symptoms could benefit the development of a pathophysiological model of symptoms such as apathy and diminished expression. Second, these pathophysiological states are likely to be influenced by different biological and environmental

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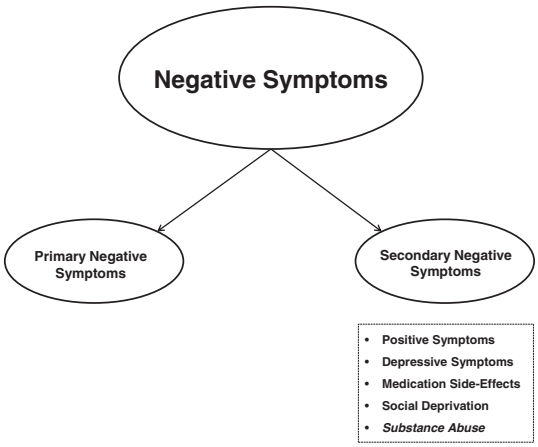

Fig. 1. Primary and secondary negative symptoms. Negative symptoms in schizophrenia can be separated in primary negative symptoms intrinsic to the disease and secondary negative symptoms caused by different underlying mechanisms. Positive symptoms, depressive symptoms, medication side-effects and social deprivation have been described as the main causes for secondary negative symptoms. Recently, substance abuse has been considered as a relevant factor for secondary negative symptoms. Several other not yet identified factors during the disease course in schizophrenia may cause negative symptoms as well.

factors depending on the type of negative symptom. The study of secondary negative symptoms can thus help to differentiate causal pathways affecting the underlying physiology. However, despite growing insights into the pathophysiology of negative symptoms, such an integrated approach for primary and secondary negative symptoms has yet to be developed (Barch and Dowd, 2010; Kirkpatrick, 2014; Kirkpatrick et al., 2001; Kring and Barch, 2014; Strauss et al., 2014). Therefore, an additional aim of this review is to consider how current neuroimaging research provides initial evidence on shared and divergent pathophysiological mechanisms of primary and secondary negative symptoms.

Finally, we recommend how future research could address secondary negative symptoms and provide an updated clinical approach to assess and treat these debilitating symptoms.

2. Methods

As mentioned above, almost all published studies on negative symptoms have focused on primary negative symptoms and have addressed secondary negative symptoms indirectly if at all. This relative lack of research and the heterogeneity of studies precluded a systematic review of studies on secondary negative symptoms. Therefore, we present a narrative review to examine the current literature of each individual cause of secondary negative symptoms. We used a two-step approach to identify relevant studies. Initially, we a searched PubMed in April 2015 using the term "secondary negative symptoms" (this retrieved 69 articles). Second, we manually searched the reference lists of these publications and of previous reviews of negative symptoms (Buchanan, 2007; Carpenter et al., 1985, 1988; Kirkpatrick, 2014; Kirkpatrick et al., 2001; Kirkpatrick and Galderisi, 2008) for additional articles not identified in the computerized search. No time span was specified for date of publication. Studies were included if they were published in a peer-reviewed journal and written in English or French. The review of all abstracts confirmed that the studies were too heterogeneous to permit a systematic review. Therefore, we decided to provide a narrative review with the goal of developing a clear structure for clinical use of the concept of secondary negative symptoms and for further research.

3. Positive psychotic symptoms

3.1. General considerations

Negative symptoms secondary to positive symptoms have been differentiated from primary or deficit symptoms (Buchanan, 2007; Carpenter et al., 1985, 1988; Kirkpatrick et al., 1989, 2001; Kirkpatrick and Galderisi, 2008). Over 30 years ago, Carpenter et al. (1985) described potential underlying psychological mechanisms contributing to this secondary effect of positive symptoms. For example, patients' experiences of threat and aversion from persecutory or paranoid thoughts may lead to social withdrawal. Furthermore, diminished expression may reflect a coping strategy in patients with dysfunctional perceptual or cognitive information processing to reduce the overwhelming experience of external stimuli.

3.2. Evidence for secondary negative symptoms due to positive symptoms

Indirect evidence has been obtained from many pharmacological trials demonstrating a correlation between positive and negative symptoms and their concurrent improvement (Chen et al., 2013; Czobor and Volavka, 1996; Kane et al., 1988; Marder and Meibach, 1994; Miller et al., 1994b; Pickar et al., 1992; Sanger et al., 1999; Szeszko et al., 2008; Tandon et al., 1993a, 1993b; Tollefson et al., 1997). Furthermore, drug withdrawal protocols have shown a correlated exacerbation of positive and negative symptoms after medication wash out (Kelley et al., 1999; Miller et al., 1994a). In addition, a longitudinal study by Tandon et al. (2000) investigating negative symptoms in initially drug-free patients with schizophrenia during their antipsychotic treatment supported the differentiation between "phasic" negative symptoms related to positive symptoms and primary enduring negative symptoms (Tandon et al., 2000).

However, studies directly investigating psychosis as a cause of secondary negative symptoms remain sparse. Importantly, most studies have not applied current definitions of negative symptoms, including the distinction between the subdomains amotivation and diminished expression. In this context, work by Kelley et al. (1999) should be highlighted; they investigated the secondary effects of medication and psychosis on negative symptoms in a double-blind haloperidol withdrawal protocol in 93 patients with schizophrenia. They reported a specific correlation of positive symptoms with the negative symptom factor amotivation but not with diminished expression. These findings strengthen the notion that psychosis as a secondary source may be related to distinct subdomains of negative symptoms.

3.3. Neuroimaging finding for secondary negative symptom due to positive symptoms

Dysfunction in the mesolimbic dopamine system has been widely recognized as a neurobiological correlate of both positive and negative symptoms (Heinz and Schlagenhauf, 2010; Howes and Kapur, 2009; Radua et al., 2015). Importantly, neural alterations in the striatum were found in studies on aberrant salience attribution describing an association with positive symptoms (Murray et al., 2008; Nielsen et al., 2012; Roiser et al., 2013; Wotruba et al., 2014) as well as in studies on reward anticipation reporting an association between blunted striatal activity and negative symptoms (Kirschner et al., 2015; Mucci et al., 2015; Radua et al., 2015; Wolf et al., 2014). However, the relationship between these neural mechanisms is far from clear, because the two approaches have usually been conducted separately. Regarding the pathogenesis of secondary negative symptoms, it would be interesting to investigate whether the mechanisms underlying blunted reward anticipation can potentially be secondary to those leading to aberrant salience attribution. Therefore, it would be important to jointly investigate aberrant salience and blunted reward anticipation in patients with different degrees of positive and negative symptoms. In addition,

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