



Negative symptoms of psychosis: A life course approach and implications for prevention and treatment

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Title: Negative symptoms of psychosis: A life course approach and implications for prevention and treatment

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Abstract

Aim: Negative symptoms are a cause of enduring disability in serious mental illness. In spite of this the development of effective treatments for negative symptoms has remained slow. The challenge of improving negative symptom outcomes is compounded by our limited understanding of their aetiology and longitudinal development.

Methods: A literature search was conducted for life course approach of negative symptoms using Pubmed. Further articles were included following manual checking of reference lists and other search strategies. The paper contains a theoretical synthesis of the literature, summarised using conceptual models.

Results: Negative symptom definitions are compared and considered within a context of the life course. Previous studies suggest that several illness phases may contribute to negative symptoms, highlighting our uncertainty in relation to the origin of negative symptoms.

Conclusions: Similar to other aspects of schizophrenia, negative symptoms likely involve a complex interplay of several risk and protective factors at different life phases. Concepts suggested in this article, such as ‘negative symptom reserve’ theory, require further research which may inform future prevention and treatment strategies.

Keywords: Negative symptoms; Psychosis; Life course approach; Prevention; Treatment.

Introduction

The aetiology of schizophrenia is complex and likely mediated by a mixture of genetic and environmental factors (Tandon, Keshavan, & Nasrallah, 2008). For some, schizophrenia can be viewed as a neurodevelopmental process which continues throughout the life course (Andreasen, 2010), with risk factors occurring both very early in life (for example obstetric complications and prenatal infection) (Cannon & Clarke, 2005), and throughout the life course (for example immigration and cannabis use) (Cantor-Graae & Selten, 2005; Large, Sharma, Compton, Slade, & Nielssen, 2011). Such a life course approach to illness has been adopted in several fields of medicine by incorporating genetics, the intrauterine environment, early life events, and events throughout the life course in an attempt to understand disease (Kuh & Ben-Schlomo, 2004). This approach provides the advantage of incorporating longitudinal aspects of disease in which both protective and risk factors are considered in detail.

Negative symptoms, a core aspect of many presentations with schizophrenia, can be defined as the absence or diminution of normal thoughts, feelings or behaviours (Buchanan, 2007). Based on factor analysis studies they can be divided into deficits of expression and motivation/pleasure (Lyne et al., 2013a), and recently developed scales have reflected this negative symptom structure (Barch, 2013; Strauss et al., 2012). Deficits of expression include affective flattening and alogia, while motivation/pleasure domain symptoms include avolition, anhedonia and asociality (Marder & Galderisi, 2017). Some studies have suggested different correlates for each domain and domain based research is ongoing (Strauss et al., 2013). Negative symptoms have classically been described in relation to schizophrenia (American Psychiatric Association, 2000), however it is also recognised that negative symptoms may occur in illnesses other than schizophrenia (Andreasen, 1987; Lyne et al., 2012).

Although negative symptoms can be among the most disabling in psychotic illness, they are often under-recognised, undertreated and are widely regarded as an unmet therapeutic need (Velligan & Alphs, 2008). Whilst negative symptoms are known to have a major impact on poor functioning, quality of life and long-term outcome (Lang, Kisters, Lang, Becker, & Jager, 2013; Milev, Ho, Arndt, & Andreasen, 2005), progression of treatments for these symptoms has remained frustratingly slow (Stahl & Buckley, 2007).

Given the limited treatment options available for treating individuals with established negative symptoms (Fusar-Poli et al., 2014), the aim of this conceptual review was to

summarise the literature relating to negative symptoms across different phases of the life course with a view to informing prevention, treatment and future research strategies for negative symptoms.

Methods

This review article begins by summarising negative symptom concepts including negative symptom definitions and classification. The main part of the review relating to the life course of negative symptoms identified references through search of PubMed for articles published from January 1971 to April 2017, by use of the terms "life course" and "negative symptoms". The search yielded 1,351 results, the abstracts of which were screened by the first author (JL). Other relevant articles were identified by manually checking the authors' personal files and the reference lists of relevant articles which yielded 662 results. Records from all searches were checked for duplicates (n = 6). Publications in English were included, and there was no specific searches conducted for unpublished studies, conference abstracts and conference presentations.

The articles were screened aiming to include all literature relating to concepts addressing the life course of negative symptoms, including genetics, neurodevelopment, premorbid negative symptoms, psychosis prodrome, early phase of illness and longitudinal course of negative symptoms. After exclusion of articles following screening of abstracts the full text of articles referring to the life course of negative symptoms were reviewed (n = 164). Following assessment for eligibility the final review paper included 68 articles which were included in a conceptual review of the life course of negative symptoms. A conceptual review was considered appropriate as the concepts under review encompass a broad research area which would be difficult to research using a systematic review search strategy. The life course approach concepts were then synthesised with consideration of clinical implications and future research. Figure 1 summarises the search strategy used for the review and is adapted from a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (www.prisma-statement.org).

Insert Figure 1 here

Negative symptom classifications

The challenge of defining negative symptoms has impeded research progress for several decades. Negative symptoms may be measured using several methods such as cross-sectional measurement, considering negative symptoms in terms of their persistence, and measuring negative symptoms that both persist and are not secondary to other sources of illness (Table 1).

Insert Table 1 here

Cross-sectional, persistent and deficit negative symptoms

Several of the most widely used symptom rating scales for schizophrenia, such as the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), and Scale for the Assessment of Negative Symptoms (SANS) measure negative symptoms at a single cross-sectional timepoint and don't take account of whether symptoms are primary or secondary to another aspect of illness (Kay, Fiszbein, & Opler, 1987; Andreasen, 1984). Newer rating scales such as The Clinical Assessment Interview for Negative Symptoms (CAINS)(Horan, Kring, Gur, Reise, & Blanchard, 2011) and the Brief Negative Symptom Scale (BNSS)(Kirkpatrick et al., 2011) take a similar cross-sectional approach. A benefit of this strategy is the convenience of measurement at only a single timepoint and ease of tracking the course of symptoms across time.

The deficit syndrome (DS) has been used to define a population of individuals with schizophrenia who have persistent negative symptoms that are not caused by factors other than the core disease process (Kirkpatrick, Buchanan, Ross, & Carpenter, Jr., 2001). The schedule for the deficit syndrome defines the DS as including enduring negative symptoms for 12 months which are not secondary to other sources of negative symptoms such as depression, positive symptoms and Parkinsonism (Kirkpatrick, Buchanan, McKenney, Alphas, & Carpenter, Jr., 1989). A diagnosis of schizophrenia must be present and negative symptoms need to persist at all times during the 12 month period, with the exception of during acute psychotic states. This contrasts with the rating scales described above which measure negative symptoms cross-sectionally, without taking longitudinal persistence into account, and without distinguishing primary from secondary negative symptoms.

Persistent Negative Symptoms (PNS) are a concept related to the DS which can be measured using commonly used research tools, such as the PANSS and SANS, at separate timepoints (Buchanan, 2007). PNS have been defined using different definitions, for which broader PNS criteria can include both primary and secondary negative symptoms (Edwards,

McGorry, Waddell, & Harrigan, 1999), while stricter criteria include only primary negative symptoms (Chang et al., 2011; Galderisi et al., 2013). In contrast to the narrowly defined DS, some PNS definitions include secondary negative symptoms, while in contrast to the more broadly defined cross-sectional negative symptoms, PNS include only symptoms which persist over time (Buchanan, 2007).

Negative symptoms have also been divided using primary and secondary classification. Primary negative symptoms are symptoms inherent to schizophrenia, whereas secondary negative symptoms are considered to be caused by other features of the disorder (Kirkpatrick, 2014). Secondary negative symptoms may arise from a range of sources occurring in psychosis such as depressive symptoms, positive symptoms, Parkinsonism and environmental deprivation (Tarrier, 2006).

Negative symptom components and aetiology

Tandon and colleagues have suggested the possibility that negative symptoms may be divided into three aetiologically distinct components (Tandon et al., 2000): (i) The phasic component which is present during the acute phase (ii) The premorbid component which is present prior to onset of illness and (iii) The deteriorative component which persists over time. The acute phase component likely represents secondary negative symptoms, and disentangling primary negative symptoms from other clinical characteristics of psychosis represents a major challenge in negative symptom research (Flaum & Andreasen, 1995; Messinger et al., 2011). The premorbid component of negative symptoms may result from poor premorbid adjustment or premorbid schizoid traits (Cuesta, Peralta, Gil, & Artamendi, 2007). The deteriorative component of negative symptoms could be regarded as a similar construct to persistent negative symptoms. Distinguishing these different types of negative symptoms with negative symptom rating scales can be difficult, and furthermore negative symptoms may often comprise a mixture of these aetiologies.

Negative symptoms across different phases of the life course

Risk and protective factors for negative symptoms occurring across different phases of the life course may be a novel approach to improving our understanding of negative symptom presentations. Negative symptom phenotypes could occur due to processes occurring during several different phases which we will consider in further detail (Figure 1).

Insert Figure 2 here

Genes and negative symptoms

The possibility that genes influence the presence of negative symptoms in schizophrenia has been proposed, and several single nucleotide polymorphisms have been associated with negative symptoms (Xu et al., 2013). A gamma-aminobutyric acid (GABA) transporter gene (Park et al., 2011), glutamatergic genes (Wirgenes et al., 2009; Bishop, Ellingrod, Moline, & Miller, 2005), and dopamine D2 receptor genes (Chien et al., 2013; Lane et al., 2004) have all been implicated with negative symptoms. Catechol-O-methyltransferase, a key enzyme for degrading dopamine in the prefrontal cortex, is another candidate negative symptom gene (Li et al., 2012; Wang, Fang, Shen, & Xu, 2010; Kang et al., 2012). Of note social anhedonia and withdrawal have been shown to be higher in unaffected siblings of patients with psychosis than in controls, supporting further that negative symptoms may be at least partially familial (Velthorst & Meijer, 2012).

Overall previous studies provide support for the idea that negative symptom presentations in psychosis can be influenced by genetic variants, although further study is needed before drawing firm conclusions. The genes implicated may involve neurotransmitters such as dopaminergic or glutamatergic pathways (Pinacho et al., 2013). Greater consideration of gene-environment interaction may be needed when studying genetic effects (van Os & Murray, 2008). The role of epigenetics is a further area in need of investigation (Rutten & Mill, 2009).

Neurodevelopment and early intrauterine development

Prenatal events are associated with later development of schizophrenia (Cannon, Jones, & Murray, 2002), and previous study has suggested that the early intrauterine environment could impact on later functioning deficits (Rehn & Rees, 2005). Models have been proposed in relation to the effects of prenatal infection or early maternal deprivation on brain development, which could have impact on negative symptoms in psychosis (Limosin, 2014). It has been suggested that corticostriatal glutamatergic transmission impacting on dopamine release could mediate cerebral damage through excitotoxicity and oxidative stress. Early neurodevelopmental abnormality could contribute to 'developmental lag' during the first two decades of life, thus contributing to poorer cognitive functioning and premorbid adjustment (Bora, 2015). The hypothalamic-pituitary adrenal axis has also been implicated in neurodevelopmental models (Limosin, 2014).

Premorbid phase of illness and premorbid adjustment

Several studies have indicated that poor premorbid adjustment is linked with negative symptoms both early in the course of psychotic illness (MacBeth & Gumley, 2008; Addington & Addington, 2005), and in more advanced presentations (Keefe et al., 1989; Kelley, Gilbertson, Mouton, & van Kammen, 1992). The precise mechanism of this important relationship is a poorly understood area requiring more investigation (Gupta, Rajaprabhakaran, Arndt, Flaum, & Andreasen, 1995; Schuldberg, Quinlan, & Glazer, 1999). The finding that negative symptoms such as motivational impairment are predictive of transition to psychosis in non-help seeking epidemiological samples highlights the importance of the premorbid period for negative symptoms, and may suggest that this is the initial onset of negative symptoms (Kaymaz et al., 2012). Some have argued that negative symptoms could, at least in some cases, represent a deterioration in premorbid schizoid traits (Peralta, Cuesta, & de Leon, 1991), and premorbid schizoid traits have been shown to predict later residual negative symptoms (Cuesta et al., 2007). Birth cohort studies have also shown that schizophrenia is preceded by cognitive deficits (Tiihonen et al., 2005), including deficits in expression of speech (Welham, Isohanni, Jones, & McGrath, 2009).

Along with poor premorbid adjustment, attachment security has also been associated with negative symptoms (Gumley et al., 2014), and traumagenic models related to early life abuse are a further consideration which could potentially be related to poor premorbid adjustment (Limosin, 2014). The contribution of genetic, neurodevelopmental and early life events to poor premorbid adjustment and early negative symptoms is an important consideration.

Negative symptoms in the psychosis prodrome and early psychosis

There are several clues that the psychosis prodrome is important to our understanding of the evolution of negative symptoms, and some novel scales in development reflect this (Pelletier-Baldelli, Strauss, Visser, & Mittal, 2017). Negative symptoms have been reported as the commonest first onset symptom in schizophrenia (an der Heiden & Hafner, 2000), and negative symptoms may be a risk factor for transition to psychosis, both in a clinical high risk and a general population (Piskulic et al., 2012; Velthorst et al., 2009; Cannon et al., 2008; Nieman et al., 2013; Maki et al., 2008). Negative symptoms are frequently reported as having onset during the putatively prodromal stage of psychosis, and these negative symptoms are associated with negative symptoms at first presentation with psychosis (Lyne et al., 2013b).

The psychosis prodrome is often characterised by symptoms which are similar to motivation/pleasure negative symptoms, such as social withdrawal and deterioration in

functioning (Iyer et al., 2008; Lencz, Smith, Auther, Correll, & Cornblatt, 2004; Yung, Phillips, Yuen, & McGorry, 2004; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005). Nonetheless, it is uncertain whether this is the initial development of the negative symptoms which are seen in later phases of illness. Although negative symptoms may often present prior to positive symptom onset (Reichenberg et al., 2005; Cannon et al., 2002; Hafner, Maurer, Löffler, & Riecher-Rossler, 1993), there has been a lack of studies focusing on negative symptoms during this early phase (Norman, Scholten, Malla, & Ballageer, 2005).

The presence of negative symptoms at baseline in individuals identified as ultra-high risk for psychosis is associated with poor functioning at longitudinal follow-up (Cotter et al., 2014). Additionally, individuals identified as ultra-high risk who subsequently develop a non-psychotic disorder were found to have more negative symptoms at baseline (Lin et al., 2015), indicating that the presence of negative symptoms in individuals identified as ultra-high risk represent a general poor prognostic factor.

While several studies have reported a relationship between duration of untreated psychosis (DUP) and negative symptoms (Boonstra et al., 2012), others describe an association between negative symptoms and both duration of untreated illness and duration of psychosis prodrome (Crumlish et al., 2009; Edwards et al., 1999). Another study has reported a relationship between negative symptoms and duration of active psychosis (DAP), a period inclusive of active psychosis during the untreated psychosis phase and post initiation of treatment (Lyne, Joober, Schmitz, Lepage, & Malla, 2017). Overall previous studies indicate that both the psychosis prodrome and active psychosis phases may contribute to negative symptom development. Further appraisal is needed in relation to whether toxic pathophysiological processes during these illness phases may contribute to development of negative symptoms (McGlashan, 2006).

Longitudinal course of negative symptoms following illness onset

Previous study of the longitudinal course of negative symptoms has yielded inconsistent conclusions. While a number of studies have reported negative symptoms to be relatively stable over time (Kulhara & Chandiramani, 1990; Pfohl & Winokur, 1983; Lindenmayer, Kay, & Friedman, 1986), others have suggested that negative symptoms may fluctuate or be reversible (Herbener & Harrow, 2001; Thara, Henrietta, Joseph, Rajkumar, & Eaton, 1994; Pogue-Geile & Harrow, 1985; Austin et al., 2015). Some studies have noted that while negative symptoms may not be prominent initially, they can accrue over time and eventually dominate the clinical picture (Mancevski et al., 2007; McGlashan & Fenton, 1992), although this view has been challenged (Kay, 1990). There is also evidence that negative symptoms are relatively high during initial presentation, but are lower at one and two year

follow-up (Mezquida et al., 2017). Studies reporting longitudinal negative symptom prevalence across separate time-periods suggest that both cross-sectional (Herbener & Harrow, 2001) and persistent negative symptoms (Chang et al., 2011) can persist for some individuals and fluctuate for others.

Evidence relating to the longitudinal relationship between positive and negative symptoms has also been mixed. Positive and negative symptoms can co-vary across time, for example with improvement of both symptoms following institution of antipsychotic medication (Czobor & Volavka, 1996; Tandon et al., 1993), however this relationship has not been consistent (Breier et al., 1987; Serban, Siegel, & Gaffney, 1992). In the longer term negative and positive symptoms likely have an independent longitudinal course (Rey et al., 1994; McGlashan & Fenton, 1992), with negative symptoms displaying greater stability over time (Kulhara & Chandiramani, 1990; Pfohl & Winokur, 1983).

Implications and future research

Why is poor premorbid adjustment associated with negative symptoms?

Although several studies have found poor premorbid adjustment to be associated with negative symptoms, the precise mechanism of this important relationship is poorly understood. There may be overlap between the definition of premorbid adjustment and negative symptoms, and premorbid adjustment items, such as ‘sociability and withdrawal’, ‘peer relationships’ and ‘scholastic performance’, may overlap with negative symptom items (van Mastrigt & Addington, 2002). This overlap would support the idea that premorbid adjustment measures a construct similar to negative symptoms in the premorbid period which could at least partially explain the significant relationship between poor premorbid adjustment and negative symptoms.

Another explanation for the premorbid adjustment relationship with negative symptoms is that poor premorbid adjustment is an early expression of a DS, representing a disease type within the syndrome of schizophrenia (Kirkpatrick et al., 2001). Previous study has provided support for DS representing a separate illness subgroup with insidious onset and poor outcome (Galderisi & Maj, 2009).

Negative symptom reserve theory

A further theory that might explain the relationship between premorbid adjustment and negative symptoms is a ‘negative symptom reserve’ theory, whereby individuals who have poor premorbid adjustment, with social and academic functioning deficits, are more vulnerable to developing severe deficits after illness onset. As discussed earlier poor social

and academic functioning may have genetic or neurodevelopmental aetiology, which may be particularly relevant if these deficits were exacerbated by the pathophysiology of psychosis. Such premorbid deficits might not be regarded as true negative symptoms, but rather they would increase vulnerability to developing negative symptoms. This concept is similar to cognitive reserve theory for dementia, which suggests that factors across the lifespan such as higher education, participation in mentally stimulating activities and complexity of occupation can increase an individual's protection against dementia (Harrison et al., 2015). Cognitive reserve theory has been mainly applied to dementia, although more recently the 'reserve' concept has also been suggested for cognitive deficits in schizophrenia (Rabinowitz et al., 2013; de la Serna et al., 2013).

Similar to cognitive reserve we suggest that a novel concept, 'negative symptom reserve', could result from more efficient premorbid brain functioning acting as a protective factor from onset of deficits in schizophrenia. In particular individuals with high levels of expression and motivation premorbidly, could be protected from negative symptom onset. A 'negative symptom reserve' theory could also explain why some individuals develop negative symptoms early in the illness, while the presence of a greater negative symptom reserve could act as a protective factor for others. Assessment of premorbid negative symptom reserve may be important when considering whether an individual has returned to baseline expression of negative symptoms, by comparing premorbid negative symptom expression with later negative symptom expression. Although a potentially helpful theory for improving our understanding of negative symptoms, 'negative symptom reserve' requires further research to be considered a valid concept. Such investigation could focus on the relationship between premorbid expression / motivation and subsequent onset of negative symptoms.

What are the correlates of 'negative symptom reserve' deterioration from the premorbid period?

Individuals with poor premorbid adjustment or low 'negative symptom reserve' could score higher on negative symptom scales prior to development of a psychotic illness. To our knowledge no previous study has retrospectively rated negative symptoms during the premorbid period and again at illness presentation to ascertain the predictors of a negative symptom deterioration from the premorbid period. Although subject to limitations, retrospective methodology may be a feasible approach for such study by measuring negative symptoms during the premorbid, psychosis prodrome and untreated psychosis phases using a modified retrospective negative symptom scale.

A further interesting avenue of investigation for negative symptom development is the role of protective factors, which may impact on negative symptom reserve. Individuals with

short duration of untreated psychosis (Boonstra et al., 2012), older age of onset (Immonen, Jaaskelainen, Korpela, & Miettunen, 2017), more years in education (Clarke et al., 2006), female sex (Leung & Chue, 2000) and married marital status (Makinen et al., 2010) have been shown to have better negative symptom outcomes. Several of these factors are stable regardless of interventions delivered, and an evaluation of whether risk or protective factors for negative symptoms are malleable is an important consideration (Harrigan, McGorry, & Krstev, 2003).

Do long-standing secondary negative symptoms result in persistent negative deficits?

Retrospective measurement of secondary sources of negative symptoms would also be of interest to determine their longitudinal relationship with negative symptom deficits early in the illness. Relationship of negative symptoms with intensity and duration of positive symptoms or active psychosis should be evaluated in further detail (Compton, Gordon, Weiss, & Walker, 2011; Andreasen, Liu, Ziebell, Vora, & Ho, 2013), and a similar approach could be taken for depressive symptoms, Parkinsonism, medication side-effects and environmental deprivation. Following on from this an interesting avenue of investigation would be to ascertain whether longstanding secondary negative symptoms develop into primary negative symptoms if they remain untreated. This could for example involve biological effects of neurotransmitters or neuroinflammation occurring with persistent presence of secondary negative symptoms.

The initial onset and early course of negative symptoms

The timing of initial onset of negative symptoms remains unclear (Lyne et al., 2015), and similar to positive symptoms (Kelleher & Cannon, 2011), our understanding of this is complicated by findings that there is a low prevalence of negative symptoms in the general population (Emmerson et al., 2009). As discussed already, there is evidence that negative symptoms may begin in the premorbid period (Kelley et al., 1992) or during the psychosis prodrome (Iyer et al., 2008), while for others negative symptoms may begin after relapses in the early psychosis phases (Wiersma, Nienhuis, Slooff, & Giel, 1998).

Although negative symptoms can have onset in the psychosis prodrome, before the onset of a positive symptom psychotic episode, it remains unclear whether negative symptoms occur prior to subthreshold positive symptoms. There is emerging evidence that negative symptoms increase risk for psychosis in a clinical high risk population (Valmaggia et al., 2013), which could be explained by negative symptoms beginning concurrently or secondary to subthreshold positive symptoms. Alternatively negative symptoms may be an inherent trait of an illness which eventually develops into a psychosis with positive

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3 symptoms, and furthermore the social and occupational isolation due to these inherent
4 negative symptoms could increase risk for psychosis.
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7 A further consideration for the longitudinal course of negative symptoms is that
8 biological improvement across time may impact on prevalence. Using an analogy of
9 traumatic brain injury, an assessment of outcome may not be possible until six months after
10 the initial injury, and ongoing recovery can occur thereafter (Maas, Stocchetti, & Bullock,
11 2008). Structural damage, inflammatory processes and neurotransmitters are implicated in
12 the neurological damage of traumatic brain injury, and if similar processes are involved in the
13 pathophysiology of negative symptoms, perhaps assessment of recovery from negative
14 symptoms also requires an interval of time. For example rehabilitative efforts may improve
15 negative symptom outcome over a period of months or even years after an initial episode,
16 while later psychotic episodes could impede recovery from negative symptoms.
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19 20 21 *Is there a critical period during the life course?* 22 23

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25 It remains unclear whether a particular phase of the life course acts as a critical
26 period over and above other phases in relation to the development of persistent treatment
27 refractory negative symptom deficits. It is possible that rather than a 'critical' period there
28 may be 'sensitive' periods in which individuals are more susceptible to developing negative
29 symptoms than at other periods. While many previous studies have investigated simple 'risk
30 chains', such as the relationship between premorbid adjustment and negative symptoms,
31 fewer studies have investigated whether an accumulation of risk factors across the life
32 course could result in negative symptoms. Alternatively early life risk factors for negative
33 symptoms could interact with later life exposures leading to negative symptom onset.
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39 40 41 *Prevention and treatment strategies for negative symptoms* 42

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44 Given the challenges in treatment of negative symptoms (Fusar-Poli et al., 2014),
45 strategies for prevention of negative symptoms could play an important role for improving
46 negative symptom outcomes across the life course. Primary prevention of negative
47 symptoms, before the onset of psychotic illness, would require population based strategies
48 which are probably best reserved for prevention of mental illness in general. However,
49 following illness onset, prevention of negative symptoms could be appropriate using
50 standardised delivery of psychosocial interventions (Thorup et al., 2005) such as supported
51 employment (McGurk & Mueser, 2004), cognitive remediation therapy (Klingberg et al.,
52 2011) and cognitive behavioural therapy (Wykes, Steel, Everitt, & Tarrier, 2008; Grant, Huh,
53 Perivoliotis, Stolar, & Beck, 2012). Given the high prevalence of negative symptoms in
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psychotic disorders, particularly schizophrenia (Lyne et al., 2012), a focus on prevention after establishing psychosis diagnosis may be important.

Antipsychotic medication

Whether medication could be used as part of a prevention focus remains unclear. A meta-analysis of 168 randomized placebo-controlled trials of interventions for negative symptoms conducted by Fusar Poli and colleagues found that most treatments led to a statistically significant reduction in negative symptoms at follow-up, including second generation antipsychotic medication, antidepressants, glutamatergic medications and psychological interventions (Fusar-Poli et al., 2014). However, consistent with observation in clinical practice, while the differences with the medication treatments reached statistical significance, none of the treatments reached the threshold for clinical significant improvements. This meta-analysis examined medications within groups, such as ‘second generation antipsychotic medication’, as opposed to individually. There is some evidence that augmentation with certain antipsychotics, such as Aripiprazole and Amisulpiride may benefit negative symptoms (Levine & Leucht, 2014; Chang et al., 2008), however it is unclear whether overall benefit is of clinical significance.

Antidepressant medication

Meta-analysis has demonstrated that antidepressant medication, in conjunction with antipsychotic medication, can also be effective for negative symptoms in individuals with an enduring schizophrenia disorder (Singh, Singh, Kar, & Chan, 2010; Vidal, Reese, Fischer, Chiapelli, & Himelhoch, 2013), however it is difficult to be certain how much the benefit of these medications might reflect their impact on secondary sources of negative symptoms. Reducing secondary sources of negative symptoms, such as persistent positive symptoms, depressive symptoms and Parkinsonism, could be important in moderating the subsequent development of more persistent negative symptoms, and research in this area is merited.

Other pharmacological and novel treatments

Other treatments with some evidence of benefit include transcranial magnetic stimulation (Dlabac-de Lange, Kneegting, & Aleman, 2010), B12 / folate supplementation (Roffman et al., 2013), 5HT3 antagonists (Khodaie-Ardakani et al., 2013), and glutamatergic agents, such as D-cycloserine (Goff, 2012). Antiinflammatory and neuroprotective agents, such as minocycline (Jhamnani, Shivakumar, Kalmady, Rao, & Venkatasubramanian, 2013; Chaudhry et al., 2012) and omega 3 fatty acids (Berger et al., 2008), have also shown some promise. It is unclear whether neuroprotective agents treat negative symptoms, or whether they could prevent their subsequent onset, which could be an appropriate use for medications with low side-effect burden.

As discussed there may be different components to negative symptoms, such as acute phase, premorbid and deteriorative. While distinguishing negative symptom components through measurement may be difficult, each type may have differing aetiologies (Tandon et al., 2000). Few previous studies have incorporated a methodology that distinguishes between the origin and life course phase of negative symptoms when evaluating treatments. One previous study evaluating whether Clozapine was specific for treating a particular negative symptom aetiology was inconclusive (Miller, Perry, Cadoret, & Andreasen, 1994). Future negative symptom treatment trials should conduct subanalyses for negative symptom domains (Aleman et al., 2016), negative symptom aetiology and life course phase of negative symptom onset.

Summary

Negative symptoms can be viewed as resulting from neurodevelopmental or neuroprogressive processes which occur at various stages throughout the life course, both before and after the onset of psychosis. Whether deterioration in premorbid adjustment before schizophrenia onset has a genetic or environmental cause is currently unclear, but could be important to our understanding of the initial evolution of negative symptoms. Negative symptoms may also have initial onset during the psychosis prodrome or later psychosis phases, although the precise reason for why negative symptoms have onset at a particular time remains elusive.

The possibility that several illness phases may contribute to negative symptoms highlights our uncertainty in relation to the origin of negative symptoms, and the reality could involve a complex interplay of several risk and protective factors at different life stages. While negative symptoms could develop across different phases of the life course and have multiple aetiologies, treatment strategies specific for each aetiology have not been evaluated in detail. Given the relatively poor efficacy reported in previous negative symptom treatment trials, consideration of prevention and treatment approaches using a life course perspective may be an important step in the study of this core aspect of psychosis.

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For Peer Review

Table 1: Negative symptom classifications

Negative symptom definition	Definition
Cross-sectional negative symptoms	Negative symptoms measured at a single timepoint. May be classified as primary or secondary. Measured with widely used scales such as the SANS or PANSS.
Persistent negative symptoms	Negative symptoms that endure for a specified duration (at least six months) as measured by two separate timepoints, or by multiple timepoints. Can include primary only or combination of primary and secondary negative symptoms. Can be measured using a variety of methods including measuring the SANS or PANSS at two or more timepoints.
Deficit syndrome	Primary negative symptoms that endure for at least 12 months. Diagnosis of schizophrenia is required. Usually measured by the Schedule for the Deficit Syndrome.

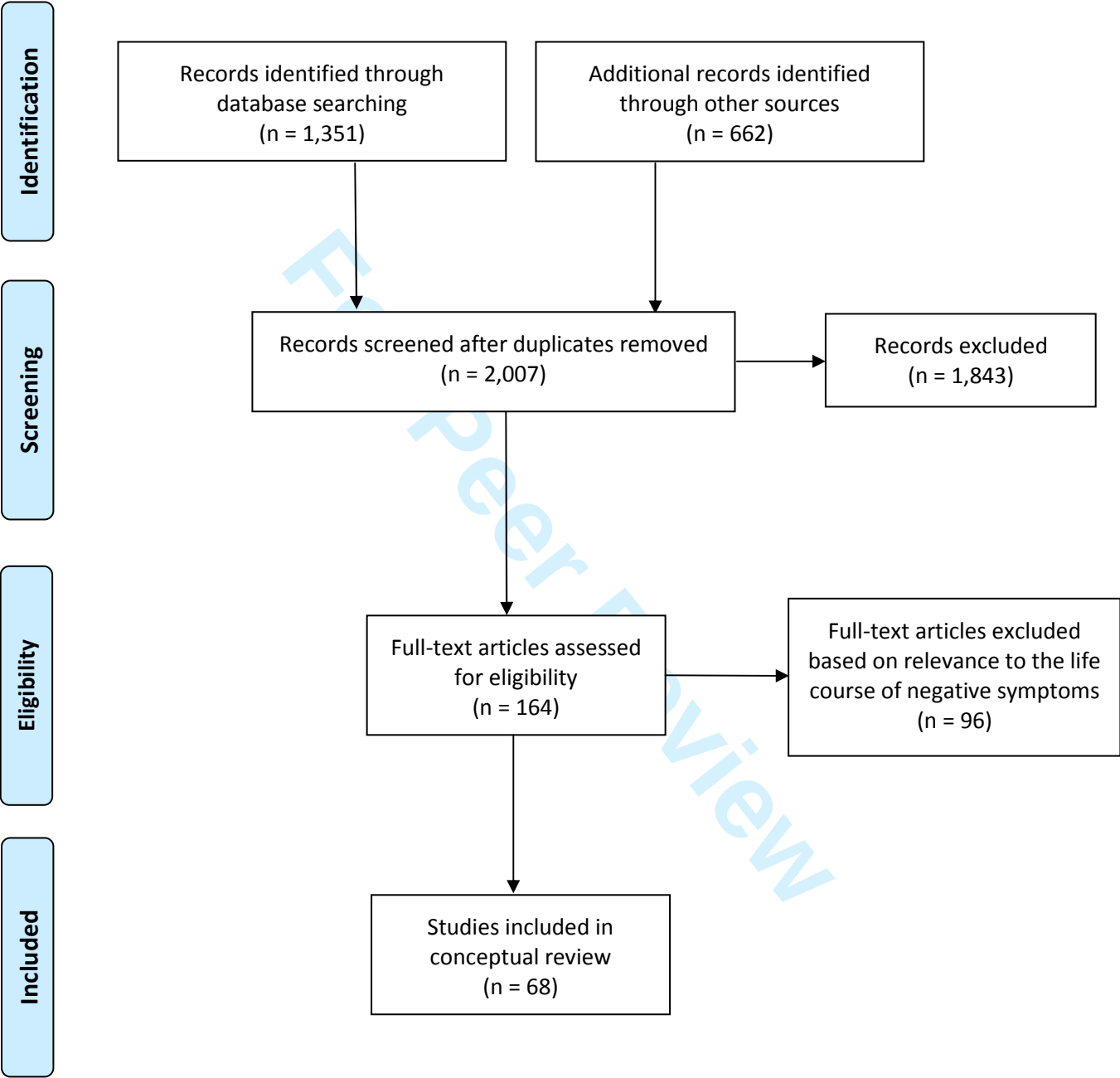


Figure 1: Flow diagram of search strategy for articles included in the study (adapted from www.prisma-statement.org)

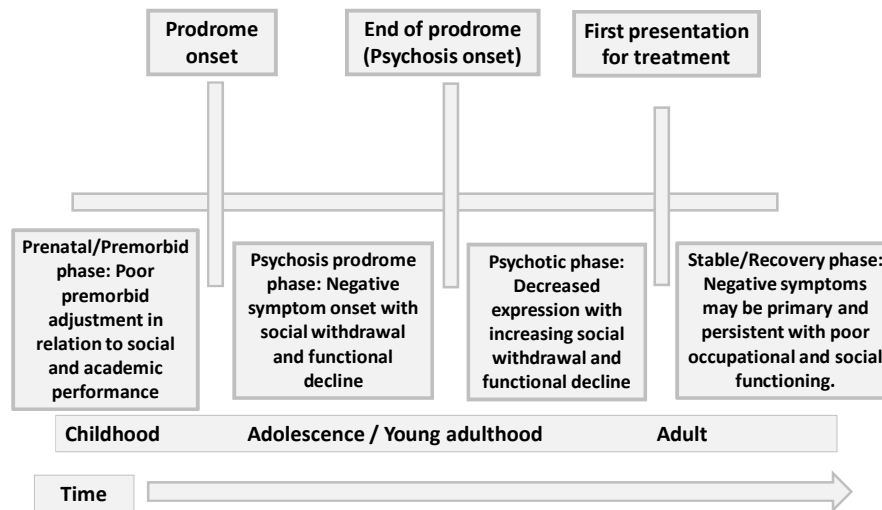


Figure 2: Negative symptoms across the phases of Schizophrenia / Psychosis