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The mediating role of depression in pathways linking positive and negative symptoms in schizophrenia. A longitudinal analysis using latent variable structural equation modelling

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Abstract

Background. The interaction between positive, negative and depressive symptoms experienced by people with schizophrenia is complex. We used longitudinal data to test the hypothesis that depressive symptoms mediate the links between positive and negative symptoms.

Methods. We analyzed data from the European Schizophrenia Cohort, randomly sampled from outpatient services in France, Germany and the UK ($N = 1208$). Initial measures were repeated after 6 and 12 months. Depressive symptoms were identified using the Calgary Depression Scale for Schizophrenia (CDSS), while positive and negative symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Latent variable structural equation modelling was used to investigate the mediating role of depression assessed at 6 months in relation to the longitudinal association between positive symptoms at baseline and negative symptoms at 12 months.

Results. We found longitudinal associations between positive symptoms at baseline and negative symptoms at 12 months, as well as between both of these and CDSS levels at 6 months. However depression did not mediate the longitudinal association between PANSS scores; all the effect was direct.

Conclusions. Our findings are incompatible with a mediating function for depression on the pathway from positive to negative symptoms, at least on this timescale. The role of depression in schizophrenic disorders remains a challenge for categorical and hierarchical diagnostic systems alike. Future research should analyze specific domains of both depressive and negative symptoms (e.g. motivational and hedonic impairments). The clinical management of negative symptoms using antidepressant treatments may need to be reconsidered.

Introduction

For the past 40 years, research on schizophrenia has distinguished the concepts of positive and negative symptoms, whether as separate syndromes of the same disease (Crow, 1980) or as dimensions on which individuals with strong positive symptom profiles differ appreciably from those with the most prominent negative ones (Andreasen and Olsen, 1982). However, negative and positive symptoms might not sit in opposition, as they may originate in the same processes (Pogue-Geile and Harrow, 1984). They may also influence each other, directly or indirectly. We recently reported that negative symptoms do not predict positive symptoms in people with established schizophrenia, whereas evidence for the opposite causal direction was ambiguous (Carrà *et al.*, 2018).

Depressive symptoms are associated with positive psychotic symptoms (Sax *et al.*, 1996), though they do not necessarily predict each other longitudinally (Yung *et al.*, 2007). The development of depression may be explained to an extent as a secondary response to the impact of schizophrenia on social status and circumstances (Birchwood *et al.*, 2005). However, it may also represent a propensity to affective dysregulation intrinsic to the schizophrenic disorder itself (Marwaha *et al.*, 2014). Certainly, depression sometimes precedes the earliest stages of psychosis (Fusar-Poli *et al.*, 2014), and specific features like anhedonia may need to be investigated transdiagnostically at a symptom level (Upthegrove *et al.*, 2017). In particular, the apparent linkage between positive and negative symptoms may include an important contribution from depressed mood, as both cross-sectional and longitudinal studies of schizophrenia confirm that negative and depressive symptoms are associated, albeit to a varying extent

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(e.g. Millan *et al*., 2014). Moreover, in periods of remission from positive symptoms, depressive and negative symptoms may be similarly associated with impaired functional recovery (Best *et al*., 2014). Assessed cross-sectionally, negative symptoms do emerge as a factor distinguishable from depression and other affective symptoms (Blanchard and Cohen, 2006). A recent systematic review has proposed that symptoms of low mood, suicidal ideation and pessimism may be more specifically related to depression, while alogia and blunted affect are specifically characteristic of negative symptoms. Anhedonia, anergia and avolition may be common to both (Krynicki *et al*., 2018). In addition, following the onset of psychosis, negative and depressive dimensions are associated with distinct patient characteristics (Quattrone *et al*., 2018), suggesting a discrimination between the two domains.

However, some studies have shown that reduction in depressed mood may lead to the alleviation of negative symptoms (Buchanan, 2007). Thus, if we accept that depression is, at least to some extent, intrinsic to the schizophrenic illness itself (Upthegrove *et al*., 2017), this might imply the existence of common aetiological factors, but also a salient role for depression in the causation of negative symptoms.

Some of the overlaps between depressed mood and negative symptoms may be conceptual, as apparent from the phenomenological problems of distinguishing them (Bosanac and Castle, 2012). However, work using Research Domain Criteria (RDoC) (Cuthbert and Kozak, 2013) does suggest significant differences between psychotic and depressive symptoms in terms of the reward-related and hedonic deficits associated with them. Thus, people with psychosis have difficulties in translating reward into action-selection whereas their in-the-moment hedonic processing is relatively intact. In contrast, these processes seem to be impaired in people with depressive psychopathology (Barch *et al*., 2016). After controlling for depression, impaired well-being in psychosis seems to be associated with the avolition-apathy negative symptom dimension, but not with the diminished expressivity reflected in blunted affect and poverty of speech (Strauss *et al*., 2012). This suggests that, at least in some clinical populations, the reduced well-being seen in individuals with negative symptoms may be independent of the psychological processes underpinning depression.

A further issue involves the effects of medication in increasing both depression levels and (by definition secondary) negative symptoms (Carpenter *et al*., 1988). Although the impact of both first- and second-generation antipsychotics on negative symptoms remains questionable (Leucht *et al*., 2009), we should take them into account in assessing the pathway between positive and negative symptoms and the role of depression.

Overall, several lines of evidence suggest that positive, depressive and negative symptoms in psychosis are distinct, but might partake in a common longitudinal pathway. The European Schizophrenia Cohort (EuroSC) provides an opportunity to test this, since it was specifically set up to compare the attributes and correlates of schizophrenia in large and representative cohorts from three European countries, France, Germany, and the UK (Bebbington *et al*., 2005).

We carried out a three-wave prospective analysis to study the potential mediating role of depression on the longitudinal interplay between positive and negative schizophrenic symptoms, based on the latent variable (cross-lagged) structural equation modelling. We hypothesized that depressive symptoms would mediate the pathways leading from positive to negative symptoms.

Methods

Participants

The EuroSC project involved a 2-year naturalistic follow-up of a cohort of people aged 18–64, suffering from schizophrenia. They were in contact with community outpatient services in three mental health catchment areas in France, four in Germany, and two in the UK. It was set up to identify and describe treatments and methods of care for people with schizophrenia, and to relate these to clinical outcomes, health conditions, and quality of life. Local ethical approval for the study was obtained in each country. The settings, sampling strategies, inclusion/exclusion criteria and demographic and clinical characteristics are fully described elsewhere (Bebbington *et al*., 2005). Eligible patients had a diagnosis of schizophrenia according to DSM–IV criteria, and had given signed informed consent. People were excluded if they had been hospitalized for the past 12 months, or were currently intoxicated, roofless or planning to leave the area (all making follow-up assessment impracticable). Information was also collected on first (FGA) and second (SGA) generation antipsychotic, and antidepressant medications. In total, 1208 people with schizophrenia participated in the study, 288 in France, 302 in the UK, and 618 in Germany.

Measures

An extensive battery of instruments was used to collect information in face-to-face interviews. Only those relevant to this study are presented here. In the UK and Germany, SCAN (Schedules for Clinical Assessment in Neuropsychiatry-version 1.0) (WHO, 1992) was used to evaluate the 4-week period before the interview and the most significant period of earlier psychopathology. Its component algorithm then allowed the establishment of diagnoses of schizophrenia. In the French centres, schizophrenia was identified using the Structured Clinical Interview for DSM-IV (Spitzer *et al*., 1992). Information on symptom profile at the different time-points was based on the 30-item interviewer-administered Positive and Negative Syndrome Scale (PANSS) (Norman *et al*., 1996). Each symptom is rated in relation to the previous 72 h on a 7-point scale. PANSS has the advantage of codifying the distinction between positive and negative symptoms (Kay, 1990). In the current analysis, we included the positive and negative sub-scores (based on items P1–P7, and N1–N7, respectively) (Kay *et al*., 1989; Addington *et al*., 1990, 1992).

Depression levels were established from the Calgary Depression Scale for Schizophrenia (CDSS) (Addington *et al*., 1990, 1992), which comprises nine items, providing scores ranging from zero to 27. It is widely used to assess depression in contradistinction to negative symptoms, as it focuses on subjective reports of hopelessness, guilt, and suicidal ideation.

Procedures

Research assistants consecutively contacted individuals from the list of potential participants, and sought their informed consent after assurance of confidentiality. Interviews took place at home or in the clinical service. The initial assessment took around 3 h, the subsequent assessments are slightly less. Participants completed standardized measures at baseline (T0) and every 6 months for the following 2 years. The current analysis used assessments at baseline (Time 0: T0), and at 6- and 12-month follow-up (T6 and T12). These intervals were chosen for analysis

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on the basis that they were clinically appropriate for investigating the mediating role of depression levels in the longitudinal interplay between positive and negative symptoms: assuming distinctness of these symptom domains, mutual relationships need sufficient time to be apparent, especially for people with the established schizophrenic illness. At the 6-month follow-up, 1024 respondents took part, while at 12-month follow-up 962 did so.

Analysis

The present study evaluated potential mediation through an autoregressive approach based on structural equation modelling in order to allow opposite paths to be estimated simultaneously (Lockhart *et al.*, 2011). Positive and negative symptoms were fitted as latent variables, while we used a single-indicator latent variable for depression in order to comply with general recommendations on mediator measurement error (Maxwell and Cole, 2007). Our measurement model was based on previous analyses of this cohort that explored whether latent positive symptoms would affect latent later negative symptoms or vice versa (Carrà *et al.*, 2018). In sum, two factors measuring positive (P1, P3–P7) and negative (N1–N6) items from PANSS yielded a measurement model with an acceptable fit, allowing us to test its structural equivalent [(χ^2 (543) = 2045.784, $p < 0.001$; CFI = 0.935; Root Mean Square Error of Approximation (RMSEA) = 0.048 (90% CI 0.046, 0.050); Standardized Root Mean Square Residual (SRMR) = 0.062]. Further details are reported elsewhere (Carrà *et al.*, 2018).

Analyses were performed using Mplus 8 (Muthén and Muthén, 2017). We used the full information maximum likelihood estimation assuming missing at random data, as initial analysis of the data showed no evidence of multivariate non-normality and there was little missing data (2% of item responses were missing across T0–T12). We fitted bivariate structural cross-lagged models in turn, to test the longitudinal associations between latent constructs for positive symptoms at baseline (T0) and negative symptoms at T12 (Fig. 1*a*); positive symptoms at baseline (T0) and depression at T6 (Fig. 1*b*); and depression at T6 and negative symptoms at T12 (Fig. 1*c*). These relationships are a precondition for inferring our hypothesized pathway via depression.

We allowed correlations between the variables and the errors of individual items over time, in order to account for consistency in item-specific variance (Cole and Maxwell, 2003). The cross-lagged paths estimate the effect of one variable on the other, after controlling for the stability of the latent constructs over time. As expected in a clinical population with established schizophrenia assessed 6-monthly, there was no indication of measurement variance (results available upon request). Nested models with constraints on the structural autoregressive paths over time did not indicate that the paths of interest (positive and negative symptoms across T0, T6, and T12) varied appreciably. This modification was therefore retained. If bivariate models showed any significant paths from either positive or negative to depressive symptoms, we fitted additional structural autoregressive mediation models.

Based on these models, we assessed total, direct and indirect effects in order to evaluate the impact of the putative mediator on the longitudinal relationship. The product of coefficients method estimated the indirect effect of positive symptoms on negative symptoms through the mediator (i.e. depression). For this, we used the Mplus MODEL INDIRECT command and relevant options. Bootstrap confidence intervals were obtained for the effects.

Following conventional recommendations (Hu and Bentler, 1999), we report three goodness-of-fit-indices. The Comparative Fit Index (CFI) represents the extent to which the hypothesized model fits the data better than a null model. The SRMR signifies the standardized difference between observed and predicted correlations for the hypothesized model. Lastly, the RMSEA assesses the extent to which the hypothesized model fits the data. Values >0.90 (CFI), and <0.08 (SRMR) and 0.05 (RMSEA) indicate an acceptable fit between models and data (Hu and Bentler, 1999). For the final models, we also calculated standardized estimates. We controlled for the potential confounding role of antipsychotic and antidepressant medications (as observed time-varying covariates), and of gender (as a time-invariant covariate). Dosages of both medication types were determined by the treating clinicians in terms of adequacy and analyzed in broad categories. Antipsychotic medication status was taken into account, including dummy variables in the model to distinguish between monotherapy and the combination of FGAs and SGAs.

Results

Table 1 shows the main sociodemographic and clinical characteristics of the sample at baseline. Participants were more often male (62%) and the mean age was 40.76 (s.d. = 10.97) years. Considerable differences in terms of length of illness were found (years: mean = 15.66, S.D. = 9.81). Attrition analyses showed no significant differences between participants with data missing at follow-up and those with complete data, on demographic characteristics or any other variables, including overall illness course ($p = 0.154$), length of illness ($p = 0.301$), and antipsychotic ($p = 0.238$) or antidepressant ($p = 0.684$) medications.

The mean scores for the psychotic symptoms and depression measures are shown in Table 2.

The average score for depressive symptoms was 2.91 (S.D. = 3.58), and only about 30–40% of participants from the three different countries reported a CDSS score higher than 3.

We first report the bivariate models. The model estimating the cross-lagged relationships between positive symptoms at baseline (T0) and negative symptoms at T12 showed a significant path ($\beta = 0.074$, $p = 0.021$), whereas there was no support for pathways in the opposite direction (Fig. 1*a*). In addition, the models quantifying the associations of the putative mediator depression at T6, with positive symptoms at baseline (T0) (Fig. 1*b*), and with negative symptoms at T12 (Fig. 1*c*), were both significant ($\beta = 0.068$, $p = 0.036$; and $\beta = 0.046$, $p = 0.043$, respectively). However, depression at T6 was also significantly associated with positive symptoms at T12 ($\beta = 0.058$, $p = 0.037$), as were negative symptoms at T6 with depression at T12 ($\beta = 0.061$, $p = 0.048$). Taken together, these bivariate analyses suggested a potential mediating role for depression.

We consequently fitted a dedicated mediation model. Figure 2 shows the structural equation model testing the longitudinal indirect effect from positive symptoms at T0 to negative symptoms at T12, via depression at T6, holding antipsychotic and antidepressant medication status as observed time-varying, and gender as time-invariant covariates.

The various cross-sectional correlations at T0 between positive, depressive and negative symptoms, were all strong and significant, as would be expected in this clinical population. In addition, the structural model showed strong and significant autoregressive

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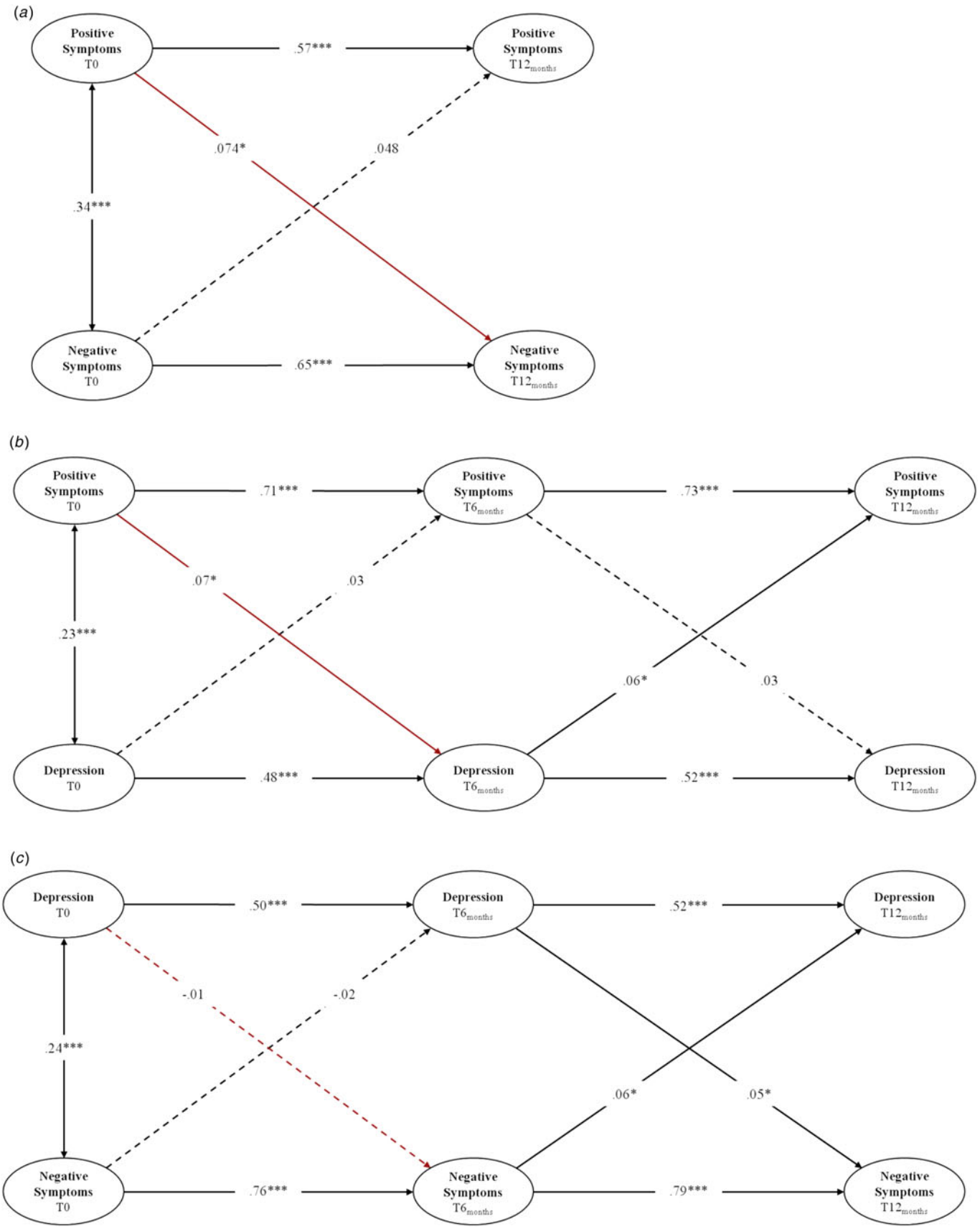

Fig. 1. Standardized structural coefficients for the bivariate models of: (a) PANSS positive at T0 and negative at T12; (b) PANSS positive at T0 and CDSS at T6; and (c) CDSS at T6 and PANSS negative at T12.

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Table 1. Sociodemographic and clinical characteristics at study entry of the study sample

	N = 1208
Male	743 (62)
Married/Living as couple	254 (21)
Living condition	
Alone	417 (35)
With partner	268 (22)
With family	295 (24)
Collective accommodation	141 (12)
Homeless	87 (7)
Ever worked	1107 (92)
Age (years), *mean* (s.d.)	40.76 (10.97)
Education (years), *mean* (s.d.)	10.12 (2.11)
Age of illness onset (years), *mean* (s.d.)	26.25 (8.37)
Length of illness (years), *mean* (s.d.)	15.66 (9.81)
Overall illness course	
Single episode, full remission	46 (4)
Single episode, partial remission	45 (4)
Episode - no symptoms	235 (20)
Episode - residual symptoms	500 (42)
Continuous	304 (26)
Other or unspecified pattern	61 (5)
With prominent negative symptoms	395 (33)
Antipsychotic medication	
FGAs	702 (58)
SGAs	291 (24)
FGAs + SGAs	159 (13)
Antidepressant medication	159 (13)

First- (FGAs) and second-generation (SGAs) antipsychotics.
Values in parentheses are percentages except as otherwise indicated.

paths over time (all *P*s < 0.001) for both latent positive and latent negative symptoms. Furthermore, the model supported a significant direct effect of positive symptoms at T0 on negative symptoms at T12 ($\beta = 0.06$, $p = 0.048$). However, when we assessed mediation via depression, positive symptoms at T0 were not associated with depression at T6 ($\beta = 0.05$, $p = 0.173$), and this in turn showed no association with negative symptoms at T12. There was consequently no significant indirect effect of positive on negative symptoms. The model showed acceptable fit to the data [(χ^2 (1168) = 3573.604, $p < 0.001$; CFI = 0.901; RMSEA = 0.041 (90% CI 0.040, 0.043); SRMR = 0.065].

Discussion

Main findings

In a large, representative cohort of people with schizophrenia, we tested the hypothesis that depressive symptoms would mediate the effect of initial positive symptoms on negative symptoms 12 months later. Even though the baseline point might relate to varying stages of disorder, all symptom types declined in frequency over this period, albeit modestly so. Although we uncovered the required associations between positive symptoms at baseline and negative symptoms at 12 months, and between both of these and CDSS depression levels at 6 months, depression could not be said to mediate the longitudinal association between PANSS scores: virtually all the effect was direct. The results from the modelling therefore did not support our hypothesis.

Interpretation of findings

Although we established a longitudinal interplay between positive and negative symptoms in our study, this was not mediated by depressive symptoms as assessed with the CDSS. Nevertheless, depression was cross-sectionally correlated with both positive and negative symptoms, as if it might be in some sense integral to schizophrenic illness (Upthegrove *et al.*, 2010), albeit distinct from core psychotic symptoms.

One of the problems of testing temporal relationships between symptoms is that it is hostage to the interval between measurements and its relationship to the temporal attributes of the causal effect. If the data collection interval is too long or too short, causal effects may be missed. This cannot be ruled out in panel studies. A recent paper using Directed Acyclic Graphs to analyze temporal relationships between affective and psychotic symptoms in the general population did identify effects operating over an 18-month period, in particular, a potential feedback loop between worry and paranoia (Kuipers *et al.*, 2019). There was however no measure of negative symptoms. The most robust way of demonstrating causal links between symptoms is by assuming that they represent psychological processes capable of direct manipulation: this approach has been adopted increasingly with psychotic conditions in the last 20 years, as reviewed by Brown and colleagues (2018). There was

Table 2. Means and s.d. for PANSS, CDSS total scores at different times

	Time 1 (baseline)			Time 2 (6 months)			Time 3 (12 months)		
	N	Mean	s.d.	N	Mean	s.d.	N	Mean	s.d.
PANSS positive	1188	12.39	5.57	1010	11.96	5.53	949	11.84	5.24
PANSS negative	1185	15.76	7.64	996	15.53	7.14	930	15.49	7.29
PANSS gen psych	1179	29.33	10.68	1013	28.18	9.93	942	28.16	9.53
CDSS	1184	2.91	3.58	1012	2.44	3.46	944	2.37	3.33

Positive and Negative Syndrome Scale (PANSS); Calgary Depression Scale for Schizophrenia (CDSS). There are missing values for some items that SEM dealt with: the greatest numbers of missing items is for T3 CDSS.

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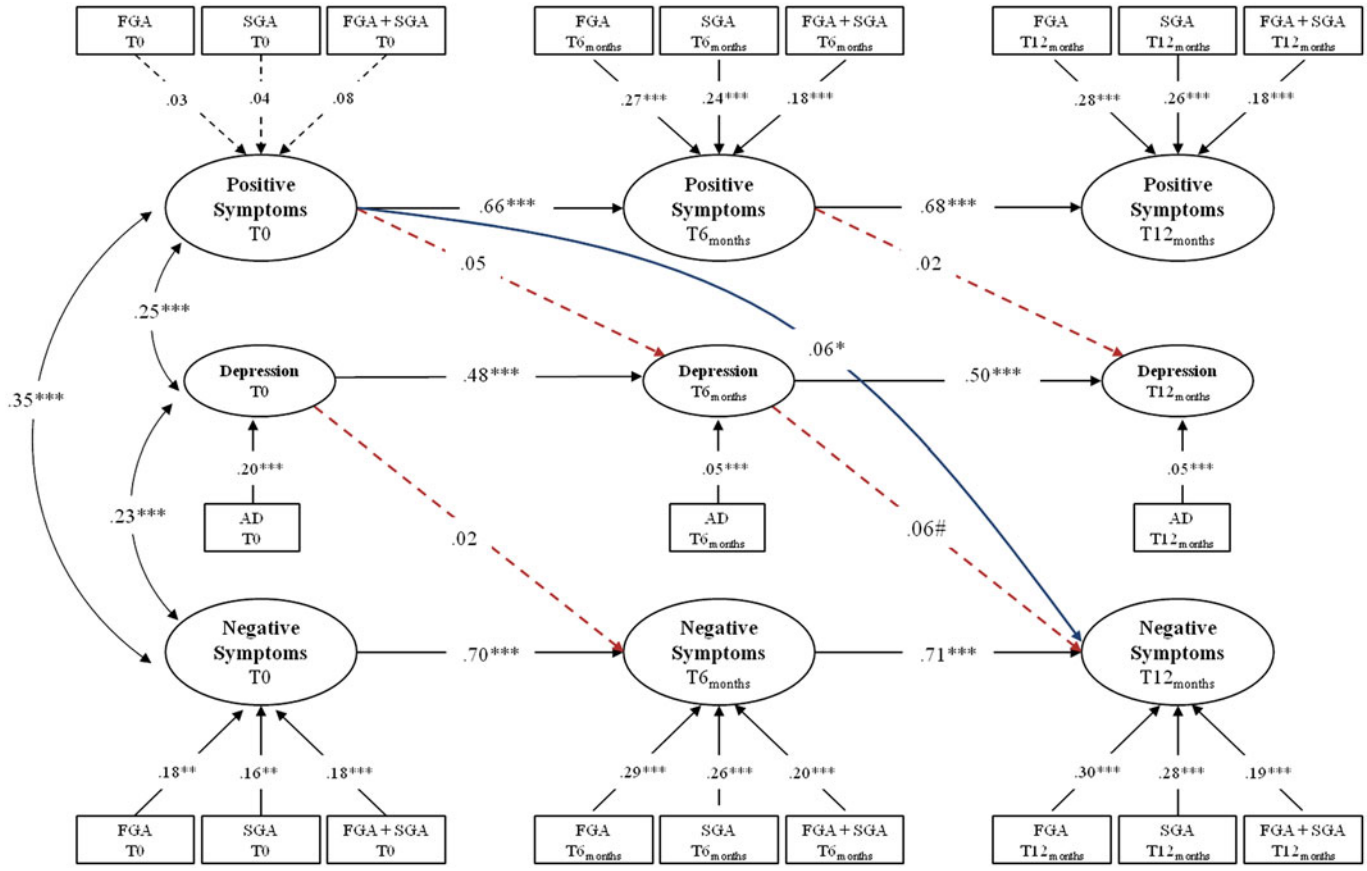

Fig. 2. Structural equation model for testing longitudinal indirect effects from positive to negative symptoms via depression levels with gender as time-invariant and both antipsychotic and antidepressant medications as observed time-varying covariates (standardized coefficients).
Ellipses represent latent variables. Rectangles represent observed (measured) time-varying covariates. Single-headed and double-headed arrows represent the effect of one variable on another and within-time correlations between pairs of latent variables, respectively. Dashed lines represent non-significant paths. T0 = baseline, T6 = 6 months follow-up; T12 = 12 months follow-up. $^{\#}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

substantial evidence relating to the effect of manipulating negative aspects of mood on paranoid ideation.

Depression in people with schizophrenia is a controversial issue in Kraepelinian categorical and hierarchical diagnostic systems (Upthegrove *et al.*, 2017), and distinguishing depressive and negative symptoms is intrinsically challenging (Bosanac and Castle, 2012). Empirically, negative symptoms resolve themselves into two factors: the first encompasses alogia and diminished expression of affect, while the second involves avolition, including anhedonia and asociality (Blanchard and Cohen, 2006). However, whereas anhedonia is common to negative symptoms and to depression, subjective reports of hopelessness, guilt and suicidal ideation may be restricted to depressive illness (Addington *et al.*, 1996). Thus depression operates through multiple pathways that are not entirely understood, and which may in part be separate from those linking psychotic symptoms. It may be better conceived through the RDoC approach to negative symptoms, with its 'positive valence' system. This proposes differences in the mechanisms of motivational and hedonic impairments across distinct diagnostic categories, including depression and schizophrenia (Cuthbert and Kozak, 2013). In particular, there seems to be a critical disparity in the nature of incentive processing impairments. Thus it appears that the pathways leading to impairments in motivated behavior in psychotic and depressive illness are different (Barch *et al.*, 2016). Impaired incentive processing in schizophrenia may be more related to compromised goal representation and utilization mechanisms than to fundamental deficits in hedonic experience (Kring and Barch, 2014). On the other hand it has been argued that, in the context of depression, altered incentive processing is more strongly linked to deficits in hedonic experience, which spread to produce impaired motivated behaviour (Liu *et al.*, 2014). Thus, whilst anhedonia broadly defined may be found in different diagnostic categories, specific sub-domains (e.g. anticipatory, consummatory, and motivational anhedonia) may be more specific (Upthegrove *et al.*, 2010), acting in concert with apathy, social withdrawal, negative self-concept (Barrowclough *et al.*, 2003), self-stigma, and poor motivation to build the core features of depression in schizophrenia (Sandhu *et al.*, 2013). This is consistent with a recent, elegant, dimensional model (albeit so far mainly based on cross-sectional evidence), which proposes a triple partition of the relationship between depressive and negative features (Krynicki *et al.*, 2018). This distinguishes symptoms spanning both depressive and negative symptoms (e.g. anergia) from those representing specific symptoms of depression (e.g. hopelessness) and negative symptoms (such as blunted affect). Future research should seek longitudinal evidence for this proposed tripartite model in people with schizophrenia. This may provide a more detailed understanding of the underlying phenomena, specifically the depressive domains that may be considered integral to schizophrenic illness. Despite our

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failure to find a longitudinal relationship between negative symptoms and the broad domain of depressive symptoms assessed by the CDSS, cross-sectional evidence from our study might nevertheless be useful for testing this tripartite model.

While our findings have implications for the conceptualization of schizophrenic processes, they also reflect on rational treatment choices. Antidepressants are prescribed to around 30% of people with schizophrenia (Mao and Zhang, 2015). The main guidelines are unclear about their use in managing depressive and negative symptoms in schizophrenia (Lehman *et al.*, 2004; Buchanan *et al.*, 2010; Barnes *et al.*, 2011; NICE, 2014). While using them carries little risk of side effects and relapse in psychosis, they have scant effect on either depressive or negative symptoms (Helfer *et al.*, 2016). Our findings indirectly support this pessimistic view of the likely effect of antidepressant prescription on negative symptoms (Fusar-Poli *et al.*, 2015), the treatment of which remains disappointing (Kirkpatrick *et al.*, 2006). Adaptations of cognitive behavioural therapy (CBT) found useful for anxiety and depression are routinely recommended for people with schizophrenia (NICE, 2014). However, CBT research in recent years has primarily focused on effects on positive symptoms, on the transition from high-risk status and, more recently, on distress. As yet no studies have targeted depression as a primary outcome (Mehl *et al.*, 2015). CBT interventions may therefore need further development to address the specific problems posed by the depressive experience in people with schizophrenia.

Strengths and limitations

Our analyses represent a significant advance over cross-sectional studies, where inferences about the directionality of association must inevitably be very tentative. While our retention of participants in the later time-points was good, attrition inevitably tends to distort the representativeness of samples. Moreover, we lacked information on reasons for refusal and drop out during the follow up. ICD-10 and DSM-IV equivalent research diagnoses for schizophrenia and the assessment of positive and negative symptoms were based on formal interviews, whilst depression was assessed by the CDSS, which focuses specifically on symptoms distinct from those that in their nature might be secondary manifestations of negative symptoms. In addition, by using the PANSS we excluded those negative symptoms with a strong *a priori* likelihood of being secondary.

Furthermore, our design, which excluded recently hospitalized subjects, would tend to reduce the likelihood of secondary negative symptoms. We controlled for time-varying levels of antipsychotic and antidepressant medication, as this might affect symptom levels differentially and hence the corresponding correlations (Sarkar *et al.*, 2015). We analyzed medication status as determined by the treating clinicians in broad categories, as a more detailed categorization would have been difficult to interpret and of questionable benefit (Leucht *et al.*, 2009).

We should acknowledge other limitations. First, we had no access to information on people who declined to participate in the study. While attempts were made to guarantee comparable recruitment procedures across the centers of the study, there will have been variations in the quality and accessibility of services (Carrà *et al.*, 2016). However, basic sensitivity analyses supported comparability between groups. In addition, although the level of depression varied considerably across our sample, the average score suggested depression at a subclinical level (Müller *et al.*, 2005). This was fairly consistent across the three national samples, but we were unable to control specifically for potential site effects, as the limited number of clusters made multilevel analysis infeasible. Future research should consider specific items in order to evaluate mechanisms operating between different types of positive and negative symptoms, given that the factor loadings assessed by SEM might not be able to uncover their unique contribution.

Finally, while our cross-lagged longitudinal models can provide information about causal ordering, the gold standard of causal inference remains targeted intervention (Kenny, 2005).

Conclusion

Our understanding of the interplay between different symptoms in schizophrenia remains limited, with corresponding limitations on treatment strategies. In particular, the nature of negative symptoms and their relationship with depression is far from fully understood despite ongoing efforts seeking biomarkers and endophenotypes. Pharmacological and other treatment strategies are likely to remain tentative until these gaps are filled. Research should also maintain a focus on non-biological factors, which have a role regardless of any underlying disease process.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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