Eur Arch Psychiatry Clin Neurosci (2018) 268:603–609
https://doi.org/10.1007/s00406-017-0813-y

ORIGINAL PAPER

Correspondence between negative symptoms and potential sources of secondary negative symptoms over time

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Received: 4 April 2017 / Accepted: 25 May 2017 / Published online: 2 June 2017

Abstract There has been a debate in the literature about the distinction between primary and secondary negative symptoms of schizophrenia. Our aim was to study the associations between negative symptoms and potential sources of secondary negative symptoms over time. A sample of 275 participants with at least mid-moderate negative symptoms was randomized into body psychotherapy or Pilates class in a previous study. No significant differences were found between groups over time and changes in the symptom domains were modest. The present investigation considers the longitudinal correlation between variables of interest at baseline, 3 and 9 months follow-up. Measures were the Clinical Assessment Interview for Negative Symptoms (CAINS), the Positive and Negative Symptom Scale (PANSS), the Calgary Depression Scale (CDSS) and the Simpson–Angus Extrapyramidal side-effects Scale (SAS). Mixed models were computed to test the longitudinal association between these variables. In a sensitivity analysis, the dosages of antipsychotic, illness duration and allocated intervention were taken into account. Overall, the course of extrapyramidal side-effects, depressive and positive symptoms was significantly related to the course of negative symptoms. Only extrapyramidal effects were longitudinally correlated to expressive negative symptoms. The sensitivity analyses showed unaltered results for positive symptoms and depression but a lack of association between extrapyramidal effects and the CAINS outcomes. In conclusion, the unambiguous interpretation between primary and secondary negative symptoms may lead to refined treatment approaches for schizophrenia and to increased effects of the interventions.

Keywords Schizophrenia · Primary negative symptoms · Depression · Positive symptoms · Extrapyramidal effects · CAINS

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Introduction

For clinical purposes, it is important to separate primary negative symptoms of schizophrenia from secondary negative symptoms, as the latter are amenable to treatment changes [1]. Primary negative symptoms comprise a core feature intrinsic to schizophrenia itself; so are considered a direct manifestation of illness pathophysiology and are more likely to be trait pathology than secondary negative symptoms [2, 3]. Secondary negative symptoms are transient; they are attributable to unrelieved positive symptoms, depression, antipsychotic-related side-effects or chronic institutionalization [4, 5]. Primary and secondary negative symptoms are similar in clinical expression, despite their contrasting aetiologies.

Among patients with schizophrenia, it is estimated that approximately 20–25% have primary negative symptoms that are sufficiently prominent to warrant clinical attention

[6]. The prevalence of secondary negative symptoms is more difficult to determine, because they arise and decline with the effects of causative factors and also because they may be superimposed over chronic or residual primary negative symptoms [7]. According to Kirschner et al. [5], secondary negative symptoms are more prevalent than primary negative symptoms and occur in more than a half of patients with schizophrenia. As an illustration, a recent meta-analysis has shown that negative symptoms are likely to improve over time providing support to the recovery model of schizophrenia [7]; but others have attributed this improvement to changes in sources of secondary negative symptoms [8]. Further studies have reported changes in negative symptoms in tandem with the improvement in positive symptoms [9, 10]; others have found the rates for negative symptoms fell to 50%, and for depression to 40%, after the remission of a first episode of psychosis and over a period of 5 years [11].

On the other hand, studies examining the factor structure of items within negative symptom scales have found evidence for two distinct domains of negative symptoms: One domain would reflect diminished expression, such as symptoms of alogia and reduced affect, and the other would represent volitional pathology with symptoms of asociality, avolition and anhedonia (e.g. [12, 13]). These findings have encouraged the development of new measures for negative symptoms: The Clinical Assessment Interview for Negative Symptoms (CAINS) [14] maps the phenomenology of schizophrenia and constructs that have been validated by neurobiological and psychological research on emotion, motivation, and affect processing [15]. The Brief Negative Symptom Scale (BNSS) has a similar structure, with one factor consisting of pleasure and motivation items, and the other including blunted affect and alogia items. The BNSS includes an item assessing the lack of normal distress not included in the CAINS [16]. Both scales include the five domains of negative symptoms (anhedonia, avolition, asociality, blunted affect, and alogia) and address expression and motivation as separable components [17]. Due to the novelty of measures including this distinction, the association between sources of secondary negative symptoms and experiential or expressive negative symptoms separately has been scarcely explored. A pioneer study showed the changes in motivation were associated with changes in depression and positive symptoms, while changes in affective flattening were associated with changes in extrapyramidal symptoms [18].

The main hypothesis of this study is that factors known to induce secondary negative symptoms in persons with schizophrenia would covary over time with different components of negative symptoms separately. The aim is to study the longitudinal association between outcomes of negative symptoms, and three potential sources of secondary negative symptoms including depression, positive symptoms, and extrapyramidal effects from antipsychotic medication. Another purpose was to explore whether the effects of antipsychotic dosage, type of intervention and years of illness duration have a role in this association.

Methods

Study design and participants

This study involved a reanalysis of data from the NESS single-blind randomized controlled trial (ICTRN842165587), approved by the Camden and Islington National Research Ethics Committee (Ref: H0722/44). Participants were randomized into a manualised, 20-session body psychotherapy group, or a 20-session beginner's-level Pilates class, in addition to standard care. Details of the main study design and rationale, as well as primary findings, were published elsewhere [19]. Two hundred and seventy-five outpatients with schizophrenia took part of this study. Participants were recruited from National Health Service mental health community teams in London and Manchester. They were eligible if they were between the ages of 18 and 65 years and had a diagnosis of schizophrenia (F20.0–F20.9) [20]. They had no change of anti-psychotic medication for 6 weeks; a Positive and Negative Syndrome Scale (PANSS) negative subscale score $\geq$18; a sufficient command of English to complete the research interviews and actively participate in group interactions in English; and an ability to give written informed consent. Participants attended significantly more body psychotherapy sessions (median = 11) than Pilates (median = 8). In total, 106 participants (75.7%) attended at least five body psychotherapy sessions [19].

Outcome measures

Assessments were conducted at three time-points: baseline, and then 3 and 9 months' follow-up. Research assistants conducting the interviews worked full time on the study and were blinded to the allocated intervention arm. The same research assistant carried out the assessments of a participant so that a positive relationship could be established.

The Clinical Assessment Interview for Negative Symptoms (CAINS) [14] was used to measure expressive and experiential negative symptoms separately. This scale consists of 13 items, rated from 0 (no impairment) to 4 (severe impairment). Nine items assess experiential deficits, involving the motivation, anticipation and experience of pleasure in occupational and recreational activities, social

contacts, friends and family. Four items relate to expressive deficits, assessing both vocal and gestural features. Evaluations of the tool suggest excellent divergent and convergent validity [21].

The Positive and Negative Syndrome Scale (PANSS) [22] was used to measure positive and negative symptoms. Its items were originally grouped into scales for positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items).The interviewers administered the PANSS as part of a structured clinical interview and scored items on a scale from 1 (asymptomatic) to 7 (extremely symptomatic). We utilized the classical approach [22] to quantify positive symptoms including: delusions, disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness and hostility. On the other hand, the negative factor approach proposed by Marder et al. [23] was adopted for the negative symptoms due to the conflation of negative and cognitive symptoms in the original subscale. In this subscale negative symptoms include blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, lack of spontaneity, motor retardation and active social avoidance.

The Calgary Depression Scale for Schizophrenia (CDSS) [24] was administered to evaluate depression. This measure has been shown to most accurately differentiate depressive symptoms from other symptoms of schizophrenia [25]. The CDSS contains 9 items ranging from 0 (absent symptomatology) to 3 (severe symptomatology) and evaluates sadness, hopelessness, self-depreciation, and guilt or suicide ideation for example; but intentionally excludes items related to motivation and anhedonia to avoid the overlap with negative symptoms.

The Simpson–Angus Extrapyramidal Side-Effects Scale (*SAS*) [26] was used to evaluate adverse effects from antipsychotic medication. This scale has ten items to measure extrapyramidal side-effects (i.e. gait, arm dropping), rated from 0 to 4, with a higher score denoting a greater severity. Given that a significant proportion of assessments were conducted in the participant's home by non-medically trained researchers, two items that required medical apparatus such as medical table (head dropping and leg pendulousness), in addition to the glabellar tap, were not administered. Therefore, the adapted summary score ranged from 0 to 28.

The Defined Daily Doses (DDD) of antipsychotic were utilized to calculate medication dosages [27]. The DDD is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug. Expression of drug use in terms of multiples of DDDs allows calculating, for each patient, a cumulative measure of drug consumption taking into account the concurrent use of more than one agent. Studies have suggested that antipsychotic doses expressed as DDDs, chlorpromazine equivalents and percentages of the British National Formulary could be reliably applied to standardize antipsychotic dosages [28, 29].

The inter-rater reliability between the assessors was high. This agreement was assessed at the beginning, middle and end of the study to ensure the scores remained sufficiently concordant throughout [19].

Statistical analysis

The statistical analysis was carried out using SPSS Statistics for Windows [30], Version 22.0. Mixed models for repeated measures were computed to study whether there is an association between the course of negative symptoms, and the course of depression, positive symptoms and extrapyramidal effects throughout the baseline, 3 and 9 months follow-ups. The models were fitted with PANSS Negative, CAINS Experiential and CAINS Expressive as dependent variables (one Model for each dependent variable), and fixed effects for the CDSS, PANSS Positive and SAS change scores. A random effect was included for participant. The role of other variables within the interplay between negative symptoms and sources of secondary negative symptoms was explored in a sensitivity analysis. The baseline outcomes of DDD of antipsychotic, illness duration and allocated intervention were included in the model as baseline covariates. To explore collinearity between DDDs and the change in the SAS, Pearson correlation was computed.

Results

Characteristics of the participants are detailed in Table 1.

Table 2 shows the longitudinal association between the change in the outcomes of negative symptoms along the baseline, 3 and 9 months follow-up and the course of depression, positive symptoms, and extrapyramidal symptoms along the same period of time. Depression change was significantly associated with the PANSS Negative and CAINS Experiential, but not with CAINS Expressive. Positive symptoms were longitudinally allied to the CAINS Experiential. Extrapyramidal side-effects (SAS) showed an association with all the outcomes of negative symptoms.

Sensitivity analysis

The Pearson correlation obtained between the DDD of antipsychotic and the SAS was positive but very weak ($r = 0.03$; $p = 0.46$) so we did not consider these variables could be collinear. When baseline covariables were introduced in the model (antipsychotic

Table 1 Characteristics of the participants on the variables studied

Variables	Baseline			3 months			9 months		
	Mean (Sd)	Min.–max.	*N*	Mean (Sd)	Min.–max.	*N*	Mean (Sd)	Min.–max.	*N*
Age	42.2 (10.7)	23–65	275	N/A			N/A		
Gender, men; *n* (%)	203 (74%)	N/A	275	N/A			N/A		
Duration of illness (years)	12.6 (9.1)	0–45	230	N/A			N/A		
Medication: defined daily dose	1.59 (1.2)	0–8	254	N/A			N/A		
CAINS experiential	2.4 (0.6)	0.8–3.8	270	2.2 (0.6)	0.4–3.9	258	2.3 (0.7)	0.2–3.9	251
CAINS expressive	1.9 (0.9)	0–4	273	1.8 (1)	0–4	260	1.7 (1)	0–4	255
PANSS negative (Marder et al.)	22.1 (4.8)	13–36	273	20.5 (5.4)	8–35	263	20.1 (5.6)	7–36	255
PANSS positive	14.1 (4.9)	7–31	273	13.2 (4.5)	7–28	261	13.5 (4.8)	7–29	255
Calgary Depression Scale	4.7 (4.3)	0–21	274	3.9 (4.3)	0–21	260	4.1 (4.1)	0–19	254
Simpson–Angus EPS^+ scale	0.3 (0.36)	0–1.86	254	0.2 (0.34)	0–1.86	247	0.2 (0.29)	0–2.3	244

Sd standard deviation, *Min.–Max* minimum and maximum, EPS^+ extrapyramidal side effects, *N* sample size

Table 2 Interplay between changes in outcomes of negative symptoms and changes in depression, positive symptoms and extrapyramidal side effects along 9 months

Outcome	Fixed effects	β (95% CI)	Sig.
PANSS negative (Marder et al.)	CDSS	0.24 (0.14 to 0.33)	$\mathbf{p < 0.0001}$
	PANSS positive	0.08 (−0.004 to 0.17)	$p = 0.064$
	SAS	2.25 (1.1 to 3.7)	$\mathbf{p < 0.0001}$
CAINS experiential	CDSS	0.03 (0.019 to 0.04)	$\mathbf{p < 0.0001}$
	PANSS positive	0.02 (0.008 to 0.03)	$\mathbf{p < 0.0001}$
	SAS	0.19 (0.05 to 0.33)	$\mathbf{p = 0.006}$
CAINS expressive	CDSS	0.004 (−0.01 to 0.02)	$p = 0.6$
	PANSS Positive	−0.007 (−0.021 to 0.007)	$p = 0.34$
	SAS	0.22 (0.032 to 0.41)	$\mathbf{p = 0.022}$

Significant associations are shown in bold

CDSS Calgary Depression Scale, *SAS* Simpson–Angus EPS scale

dosage, allocated intervention and illness duration), the association between the SAS and the CAINS expressive became non-significant. The longitudinal association between the course of negative symptoms and that in positive and depressive symptoms remained unaltered (Table 3).

Discussion

In this study, the course of negative symptoms appeared to be linked to the course of potential sources of secondary negative symptoms. Our findings showed longitudinal associations between depression and PANSS Negative and CAINS experiential. The course of positive symptoms was associated with the experiential domain of the CAINS. These results were not modified when accounting for the dose of antipsychotic, type of intervention or years of illness duration. The change in extrapyramidal effects was longitudinally associated to all the outcomes of negative symptoms; but when controlling for baseline covariates this interplay was not evident for the CAINS domains.

Depression

It has been reported over 60% incidence of depressive symptoms in schizophrenia [31]. The duration of depression in psychosis has been linked to negative symptoms, and the number of depressive symptoms has been associated to both negative and positive symptoms [32]. However, due to the symptom overlap between depression and negative symptoms, and the impairments in the ability to express inner experiences and emotions in patients with schizophrenia, it is often challenging to distinguish them [2]. According to our results, depressive and negative symptoms would show an overlap within the amotivational domain and relate throughout the features

Table 3 Longitudinal interplay controlling for antipsychotic dosage, intervention allocation and illness duration

Outcome	Fixed effects	β (95% CI)	Sig.
PANSS negative (Marder et al.)	CDSS	0.26 (0.15 to 0.38)	**$p < 0.0001$**
	PANSS positive	0.09 (−0.0004 to 0.19)	$p = 0.06$
	SAS	1.7 (0.43 to 3)	**$p = 0.009$**
	Antipsychotic dose	0.43 (−0.07 to 0.93)	$p = 0.09$
	Illness duration	−0.01 (−0.07 to 0.06)	$p = 0.6$
	Allocation[a]	0.03 (−1.15 to 1.22)	$p = 0.95$
CAINS experiential	CDSS	0.03 (0.02 to 0.05)	**$p < 0.0001$**
	PANSS Positive	0.02 (0.011 to 0.04)	**$p < 0.0001$**
	SAS	0.16 (−0.001 to 0.33)	**$p = 0.048$**
	Antipsychotic dose	0.01 (−0.06 to 0.07)	$p = 0.74$
	Illness duration	0.003 (−0.05 to 0.08)	$p = 0.52$
	Allocation	0.07 (−0.9 to 0.22)	$p = 0.41$
CAINS expressive	CDSS	−0.005 (−0.02 to 0.14)	$p = 0.62$
	PANSS Positive	−0.012 (−0.03 to 0.004)	$p = 0.14$
	SAS	0.19 (−0.02 to 0.4)	$p = 0.08$
	Antipsychotic dose	0.08 (−0.01 to 018)	$p = 0.1$
	Illness duration	0.003 (−0.01 to 0.02)	$p = 0.7$
	Allocation	−0.07 (−0.09 to 0.22)	$p = 0.94$

Significant associations are shown in bold

[a] Allocation: body psychotherapy vs. pilates

of avolition and anhedonia, which are present in both psychopathologies. This supports the study by Kelley et al. [16] suggesting that diminished motivation is associated with mood effects independently of medication effects. According to the review by Kirschner et al. [5], the occurrence of negative symptoms secondary to depression has been mainly linked to avolition and lack of energy; which may explain behaviours such as withdrawn and decreased amount of activities. This association has been found to vary between different disease stages, although some studies have reported similar prevalences of depression in patients undergoing their first episode and those with chronich schizophrenia [5]. These findings need some attention and stress the importance of employing comprehensive instruments within clinical trials. For example, the active ingredients improving depression may not be those enhancing the levels of negative symptoms, and distinguishing between them will benefit the reliability of treatment approaches. The CDSS has shown to precisely differentiate depressive symptoms from other symptoms of schizophrenia as it has been recommended as a standard instrument [31, 33].

Positive symptoms

In the present research, positive symptoms were related to the experiential domain of the CAINS. Potential underlying psychological mechanisms contributing to secondary negative symptoms would be patients' experiences of threat and aversion which led to social withdrawal; or individuals who are distracted by auditory hallucinations are less able to engage in community activities [2]. Previous studies have illustrated the improvement in positive symptoms leading to an improvement in negative symptoms [9, 10]. Others suggested this relationship was dependent on the antipsychotic treatment and not present in naïve patients [34]; but further investigation in initially drug-free patients showed a differentiation between phasic negative symptoms related to positive symptoms, and primary enduring negative symptoms [35]. The present research is derived from an intervention context which may also facilitate synergistic changes and different symptom domains may depend on each other through a unified upstream pathological disease process [10]. This has been reflected in the CAINS experiential, which evaluates the motivation to carry out a number of activities with other people and the enjoyment derived from them. Positive symptoms seem to impede the predisposition to meet other people or to enjoy from group activities. Thus, assessing particular items of paranoia, hallucinations and suspiciousness may help to understand the presence of behaviours such as social and emotional withdrawn to recommend the adequate treatment for positive or negative symptoms.

Extrapyramidal symptoms

Experiential and expressive negative symptoms appear to be influenced by extrapyramidal effects but this was not directly related to the dosage of antipsychotic. Neither extrapyramidal symptoms appear to be collinear with the dose of antipsychotic medication received. This result, although unexpected, is supported by a previous study with healthy volunteers taking one dosage of haloperidol or risperidone who did not show any significant motor extrapyramidal effect as measured with the SAS, but did report other negative symptoms (i.e. drowsiness) [36]. Additionally, it has been suggested that patients with affective flattering are more susceptible to medication effects and extrapyramidal side-effects, which was attributed to these behavioural manifestations could have a similar source [18]. However, in the present research we have found a longitudinal association of extrapyramidal effects with both experiential and expressive negative symptoms. When doses of antipsychotic, intervention allocation and duration of the illness were controlled, this interplay did not remain significant although it showed a statistical tendency. Possible explanations for these results include the side-effects of antipsychotics may be augmented in patients taking higher doses of typical antipsychotics, who receive less intensive physical activity, and/or they have motor deficits aggravated by sedentary life-styles along years of illness duration. Nonetheless, the cause of the extrapyramidal effects is not clear in the context of the present study but these appear to be closely associated to negative symptoms over time. Their assessment represented a useful insight showing to be the only source of secondary negative symptoms longitudinally correlated with both experiential and expressive negative symptoms. Therefore, to clarify whether negative symptoms of schizophrenia are primary or secondary, extrapyramidal symptoms should be taken into account.

This study has limitations to be mentioned: The observed associations in the analysis are correlational rather than causal so the assumed direction between variables is based on previous evidence and theoretical background. Changes in the various symptoms domains were relatively modest so the study of their associations does not take into account significant variation over time. The variables studied were measured three times along 9 months which is probably not long enough to draw conclusions. The doses of antipsychotic medication calculated with DDD are not a conventional measure and the specific medications are not used in their equivalence e.g. to chlorpromazine. Antipsychotics vary in the liability of extrapyramidal effects and this could not be captured within DDD. Additionally, cognition was not assessed although this may be a potential source of secondary negative symptoms and should be taken into account in future research [31].

In conclusion, negative symptoms have been recognized as a separate domain of psychopathology from positive symptoms [37–39] and to have an inconsistent overlap with depression [11, 16, 21]. The present research suggests that both positive and depressive symptoms may be source of secondary negative symptoms in stable patients with schizophrenia, and that reducing extrapyramidal effects may also help to improve secondary negative symptoms. This research provides evidence relevant to the "pseudospecificity" problem reflected in the inability to differentiate between primary and secondary negative symptoms within clinical trials [6, 8, 40]. To date, any advances in the treatment of schizophrenia have been found to provide only limited benefits to negative symptoms [40, 41]; with this study we ratify that unambiguous interpretations between primary and secondary negative symptoms may be essential to refine and improve treatments and clinical trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Financial support The data was collected as part of the NESS study, a trial funded by a grant from the National Institute for Health Research-Health Technology Assessment programme (REF: 08/116/68). The funding source had no role in the present study design, analysis, interpretation or manuscript submission.

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