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Cognitive functioning in patients with first-episode psychosis stratified by level of negative symptoms: A 1-year follow-up study

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ABSTRACT

We investigate negative symptoms over a 1-year follow-up period with the objective to see how groups defined according to level of symptom severity are related to cognition.

Eighty-seven participants with first-episode psychosis (FEP) and matched healthy controls were assessed at baseline and follow-up. FEP participants were sub-grouped based on negative symptom items from the Positive and Negative Syndrome Scale (PANSS-R) with either no, mild, transitory or sustained symptoms over one year. Following an overall MANOVA, groups were compared on cognitive domains and a cognitive composite using ANOVAs. Cognitive course was explored with a MANOVA.

We found a group effect on cognition. Participants who sustained negative symptoms were significantly outperformed by participants with no negative symptoms on executive functions and processing speed, and by those with mild or transitory symptoms on verbal learning and memory. Participants with sustained negative symptoms performed significantly poorer on the cognitive composite than those with no or mild negative symptoms. The group with no negative symptoms did not differ significantly from healthy controls on any cognitive measure, and the groups did not differ in cognitive course.

Early course of negative symptoms is associated with cognition and could guide clinicians when evaluating need for cognitive assessment.

1. Introduction

Schizophrenia is a severe mental disorder with considerable heterogeneity in terms of symptom formation, clinical course and functional outcome (Andreasen et al., 1995; Insel, 2010). Two important sources for this heterogeneity are differences in cognitive and negative symptoms. Cognitive and negative symptoms are both considered core features of schizophrenia (Green et al., 2000; Kahn and Keefe, 2013; Tandon et al., 2009) with significant impacts on functional and clinical outcome (Bowie and Harvey, 2006; Green, 1996; Lepage et al., 2014). The current classification systems allow for a psychotic disorder diagnosis, including schizophrenia, in the absence of both impaired cognition and negative symptoms (American Psychiatric Association, 2013; World Health Organization, 1993), even though studies show that these symptoms are common (Bobes et al., 2010; Keefe and Fenton, 2007). Moreover, studies across different cohorts and sampling methods, consistently report significant low to moderate correlations between cognitive and negative symptoms (Lin et al., 2013; Milev et al., 2005; Ventura et al., 2009). More specifically, findings from meta-analyses show an association between severity of negative symptoms and a wide range of cognitive domains, including impairments in memory, attention and executive functions (Aleman et al., 1999; Harvey et al., 2005; Hovington and Lepage, 2012; İnce and Üçok, 2018). Research has suggested that cognitive and negative symptoms may share a common underlying pathophysiology (Balu et al., 2012). However, findings from clinical studies are mixed. Some studies have not found cognition to improve following improvement in negative symptoms (Bell and Mishara, 2006), while a more recent meta-analysis found cognitive remediation to have a positive effect on negative symptoms (Cella et al., 2017).

One approach to investigate heterogeneity is to focus on subgroups. Cognitive subgroups have mainly been investigated in cross-sectional designs using various methods. For instance, data-driven clustering methods have been used to investigate cognitive heterogeneity in

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samples of both schizophrenia and bipolar participants (Hill et al., 2002; Lewandowski et al., 2014). These studies have found that participants belonging to the cluster with the poorest cognitive performance also have higher levels of negative symptoms. Research investigating negative symptom subgroups has focused on symptom stability using longitudinal data. Most notable is the concept of deficit schizophrenia (Carpenter et al., 1988) and the related and more recent concept of persistent negative symptoms (Buchanan, 2006; Mucci et al., 2017). Both approaches specify a defined level of negative symptoms and a minimum time of duration. Further, they include criteria to exclude negative symptoms that are secondary to depression, positive symptoms (e.g. withdrawal caused by persecutory delusions) or extrapyramidal side effects. Galderisi et al. (2013) compared patients meeting criteria for persistent negative symptoms to a control group of participants with similar baseline levels of negative symptoms which did not persist over one year. Persistence of negative symptoms was associated with poorer psychopathological outcome and worse global functioning after one year of treatment. There were, however, no group differences in cognitive functioning. This is in line with findings from a similar Chinese study (Chang et al., 2011). These studies suggest that persistence of negative symptoms is not associated with poorer cognitive functioning. They did, however, not explore the full breadth of variation of negative symptoms evident in participants with schizophrenia and related psychoses.

The first objective of the current study was to investigate how levels of negative symptoms, from complete absence to sustained levels above moderate severity, relate to cognitive functioning. To achieve this, we used longitudinal data and a novel stratification method with four levels of negative symptom severity to define subgroups. These subgroups were based on clinically meaningful cut-off values over the 1-year follow-up period. Inspired by previous research, two groups were defined as having significant symptom levels, which were either sustained or transitory over the 1-year follow-up. The remaining sample was divided in two groups to separate those who never presented with any symptoms and those who presented with only mild symptom severity. We hypothesized a dose-response relationship between cognitive function and severity of negative symptoms, with the largest differences between those who sustained significant levels of negative symptoms and those who never exceeded normal limits on any symptom item.

The second objective was to investigate whether there are differences in cognitive course between the negative symptom groups over the first year of treatment.

Finally, our third objective was to investigate the continuous relationship between cognition and negative symptoms. This was done cross-sectionally at both time points, and longitudinally by investigating how changes in negative symptoms related to changes in cognition in the entire clinical sample.

2. Methods

2.1. Participants

All participants are part of the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT), which is a large prospective cohort study. Participants with first-episode psychosis (FEP) were included between 2004 and 2012 from in- and outpatient psychiatric units at four hospitals in Oslo, Norway, covering a catchment area of about 485,000 inhabitants. FEP is defined as recruitment into the study within the first 52 weeks after start of first adequate treatment (i.e., antipsychotic medication in adequate dosage or hospitalization in a psychiatric ward treating psychosis).

Based on the 1-year follow-up diagnosis (Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)(American Psychiatric Association, 2000) we restricted the current sample to participants within the broad schizophrenia spectrum (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychosis not otherwise specified (NOS)). Because major depressive disorder (MDD) meeting the A-criterion for schizophrenia can be the start of a schizoaffective disorder these participants were also included from baseline (Andreasen et al., 2005).

Exclusion criteria were IQ < 70, head injury requiring hospitalization and/or treatment, neurological disorder, unstable or uncontrolled medical condition interfering with brain function and age beyond the range of 18–65 years. Adequate Scandinavian language skills were required to ensure validity of self-report and cognitive assessment. Substance abuse was not an exclusion criterion unless participants were under the influence on the day of assessment.

The sample initially consisted of 210 FEP participants with broad schizophrenia spectrum and MDD with psychosis at baseline. Of these, 138 participants completed follow-up assessment, resulting in a retention rate of 66%. Sixteen participants with baseline MDD did not meet criteria for broad schizophrenia spectrum disorder at 1-year follow-up and were therefore excluded (11 had MDD and five met criteria for a bipolar disorder), one participant was excluded due to head injury and 34 participants had missing data from cognitive or clinical assessment necessary for the analyses. This resulted in a final sample of 87 FEP participants. There were no differences in relevant clinical and demographic characteristics between those included in the study and those who were not (n = 123), except for the PANSS total score where included participants scored slightly higher (65 vs. 61, t = 2.03, p = .04). The 87 FEP participants were then matched on age and gender to 87 healthy controls that had complete cognitive assessment at both baseline and 1-year follow-up. These healthy controls were randomly selected from population records in the same catchment area as the FEP participants and recruited by letter of invitation. In addition to the listed exclusion criteria for FEP participants, healthy controls were excluded if they met criteria for substance abuse or dependency in the last six months or if they, or any of their close relatives, had a lifetime history of severe psychiatric disorder. All participants gave written informed consent following a complete description of the study, which was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Clinical assessment

Diagnoses were based on the Structural Clinical Interview for DSM IV Axis I disorders (SCID-I) (First et al., 1995) and difficult cases were presented in consensus meetings supervised by an experienced clinical expert for validation. The diagnostic interviews were conducted by clinical psychologists, psychiatrists or psychiatric residents who underwent training from a program developed at UCLA. Inter-rater reliability has previously been evaluated and found satisfactory with overall agreement for DSM-IV diagnostic categories of 82% and an overall κ of 0.77 (95% CI: 0.60–0.94) (Ringen et al., 2008). Based on information obtained from interviews and available medical records the duration of untreated psychosis (DUP) was estimated as weeks from onset of psychosis until start of adequate treatment. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess symptoms at baseline and 1-year follow-up. Negative symptom items were used for stratification into subgroups whereas the remaining symptom domains from PANSS were measured using the positive, disorganized and excited factors from the Wallwork five factor model (Wallwork et al., 2012). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1996). Severity of alcohol and drug use over the past year was measured with The Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT) (Hildebrand and Noteborn, 2015). Level of global functioning was measured with The Global Assessment of Functioning Scale Split version (GAF-f) (Pedersen et al., 2007).

Table 1
Comparison on sociodemographic and clinical variables at baseline between participant groups.

Variable	1. SNS	2. TNS	3. MNS	4. NNS	F/χ^2	*df*	*P*
N - 87 total (%)	26 (30)	23 (26)	26 (30)	12 (14)			
Age (yr)	26.3 ± 6.3	26.9 ± 6.2	28.1 ± 9.4	27.0 ± 9.5	0.25	3	0.9
Women *N* (%)	4(15)	15(65)	10(38)	6(50)	13.16	3	**0.004**
Education (yr)	12.5 ± 2.7	12.3 ± 2.9	12.4 ± 2.1	11.8 ± 2.0	0.91	3	0.4
IQ	96.6 ± 16.2	99.3 ± 16.4	107.0 ± 11.3	108.9 ± 10.7	3.51	3	**0.02**
Age at onset (psychosis)	23.1 ± 4.9	21.9 ± 6.0	24.7 ± 9.1	24.0 ± 7.5	0.71	3	0.5
Duration of untreated psychosis (Log)	1.7 ± 0.7	1.9 ± 0.7	1.5 ± 0.9	1.6 ± 0.9	0.97	3	0.4
PANSS positive	10.4 ± 4.2	11.6 ± 3.4	10.2 ± 3.7	12.2 ± 4.9	1.06	3	0.4
PANSS disorganized	6.8 ± 2.2	5.4 ± 2.7	5.5 ± 2.6	5.2 ± 1.9	2.06	3	0.1
PANSS excited	5.5 ± 1.6	5.9 ± 1.9	5.3 ± 2.2	6.6 ± 1.9	1.53	3	0.2
AUDIT	9.6 ± 10.4	5.6 ± 6.0	6.2 ± 5.9	9.0 ± 7.3	1.69	3	0.2
DUDIT	10.6 ± 11.9	3.1 ± 6.5	6.5 ± 10.2	3.3 ± 6.4	1.37	3	0.3
Antipsychotic medication (DDD)	1.1 ± 0.9	0.9 ± 0.7	0.9 ± 1.1	0.7 ± 0.7	0.92	3	0.4
GAF-F	36.2 ± 7.3	43.1 ± 12.3	49.0 ± 16.1	43.7 ± 11.5	4.75	3	**0.004**
Depression (CDSS total)	6.9 ± 4.5	7.6 ± 4.4	5.2 ± 3.8	3.9 ± 3.8	2.74	3	**0.05**
Schizophrenia *N* (%)	24(92)	16(70)	11(42)	7(58)	–	–	–
Schizophreniform *N* (%)	–	1(4)	2(8)	1(8)	–	–	–
Schizoaffective *N* (%)	1(4)	4(17)	3(12)	2(17)	–	–	–
Psychosis NOS *N* (%)	2(17)	10(38)	2(9)	1(4)	–	–	–

Abbreviations: Values are mean ± SD unless otherwise specified. SNS = sustained negative symptoms; TNS = Transitory negative symptoms MNS = low negative symptoms; NNS = no negative symptoms; DDD = Defined Daily Dosage. Daily dosage divided by recommended daily dosage; AUDIT = Alcohol Use Disorders Identification Test; DUDIT = Drug Use Disorders Identification Test; GAF = Global Assessment of Functioning.

2.3. Definition of negative symptom groups

Items N1, N2, N3, N4, and N6 from the PANSS negative symptom subscale were selected for subgrouping participants as these items measure core negative symptoms (Marder and Galderisi, 2017). To stratify participants, four levels of negative symptom severity were defined.

1 Sustained negative symptoms (SNS): Participants with at least one item ≥4 at *both* time points: 26 individuals
2 Transitory negative symptoms (TNS): Participants with at least one item ≥4 at only one time point: 23 individuals
3 Mild negative symptoms (MNS): Participants with at least one item =3 at one or both time points, and no item ≥4: 26 individuals
4 No negative symptoms (NNS): Participants with no item > 2 at either time point: 12 individuals

The NNS and MNS group are defined by the upper boundary of 2 and 3 respectively. This is to separate participants who never exceed normal limits from those who present mild symptoms. The value of 3 on the PANSS is also the upper limit for meeting remission criteria (Andreasen et al., 2005) which have been widely used and validated for sensitivity and specificity (Opler et al., 2007). The MNS group is thus defined for participants who vary up to a level indicating symptoms, but in such a mild degree that it falls below the normal threshold used in studies focusing on negative symptoms and is in line with remission status. The value of ≥ 4 as a cut-off for the SNS and TNS groups was used because set because it is in line with studies investigating similar negative symptom subgroups (Buchanan, 2006; Mucci et al., 2017).

2.4. Cognitive assessment

The following measures of cognition were included: The abbreviated Wechsler intelligence scale WASI was used for measure of *current IQ* (Wechsler, 1999). *Verbal learning and memory* was assessed with the California Verbal Learning Test (CVLT-II) (Delis et al., 2000) with subscores from verbal learning and recall, and with the Logical Memory, immediate and delayed recall, from the Wechsler Memory Scale (WMS) (Wechsler, 1997). *Processing speed* was measured using the Digit Symbol Test (WAIS-III), and the Color Naming and Word Reading subtest of the Color-Word Interference Test of the Delis-Kaplan Executive Function Scale (D-KEFS) (Delis et al., 2001). *Attention* was assessed using the Digit Span and Letter-Number Sequencing Test (Scale, 1997). *Executive Functions* was measured using the Inhibition and Inhibition/Switching subtests from the Color-Word Interference Test and Letter Fluency, Category Fluency and Category Switching from the Verbal Fluency Test from the D-KEFS test battery (Delis et al., 2001). All cognitive assessments were carried out by psychologists with specific training given by experienced seniors at the center. Some participants had missing test scores on one of the two time points. We handled these missing scores by imputing the known raw score from the other time point, based on recommendations for imputation in longitudinal studies (Engels and Diehr, 2003). Imputed values constitute 3.2% and 0.1% of verbal learning and memory scores at baseline and follow-up respectively, 0.8% of attention scores at baseline, 0.3% of executive functioning scores at baseline and 0.2% of processing speed scores at follow-up. *Z*-scores were calculated for all neuropsychological tests using baseline means and standard deviations of the matched healthy control sample. Tests where higher values reflect poorer performance were inverted. As an index of general cognitive ability across cognitive domains we calculated a cognitive composite score as an average of the *Z*-score for all 14 tests. Scores for the above-mentioned cognitive domains were calculated by averaging the *Z*-scores for tests in the respective domain.

2.5. Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, version 25. Data were checked for normality, homogeneity of variance and outliers. The AUDIT, DUDIT, DUP and DDD variables were skewed and therefore log-transformed. One-way analyses of variance (ANOVAs) and Chi squared tests were conducted to compare the four negative symptom groups on demographic and clinical variables. Alpha level was set at $p < .05$. Clinical and demographic data are presented in Table 1.

2.5.1. Analysis of baseline differences in cognition

To investigate our first aim we first performed a multivariate analysis of variance (MANOVA) as an omnibus test with the four cognitive domains as dependent variables. Negative symptom group, including healthy controls, was entered as the independent variable. We then controlled for possible confounders by following up with a total of six multivariate analyses of covariance (MANCOVAs), correcting for age,

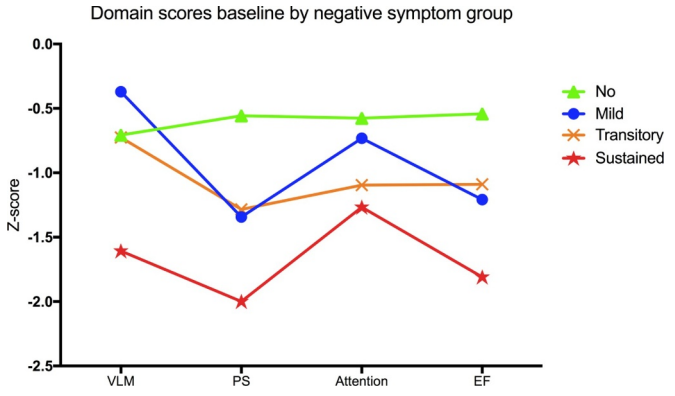

Fig. 1. VLM = Verbal learning and memory; PS = Processing speed; EF = Executive functions.

gender, positive symptoms, depression, antipsychotic medication and IQ by entering these variables as covariates. Healthy control participants were not included in the MANCOVAs correcting for positive symptoms, antipsychotic medication and depression.

Following a significant result on the omnibus MANOVA, 4 separate ANOVAs were conducted to explore the between-group effect of negative symptom group on cognition. The four cognitive domains were entered as dependent variables. To investigate the level of general cognitive ability, we also performed an ANOVA investigating the effect of negative symptom group on the cognitive composite score. Sidak corrected post-hoc comparisons were performed for all significant ANOVAs to explore pairwise between-group differences. Between-group effect sizes were calculated and are reported as Cohen's *d*, where $d = 0.2$ is considered small, $d = 0.5$ medium and $d = 0.8$ large (Cohen, 1988).

2.5.2. Analysis of cognitive course

To investigate the second aim, comparing cognitive course between the negative symptom groups and healthy controls, we calculated individual change scores for each of the four cognitive domains by subtracting the values at baseline from the 1-year follow-up. The cognitive change scores for each domain were then used as dependent variables in a MANOVA with negative symptom group as the independent variable.

2.5.3. Analysis of the continuous relationship between cognition and negative symptoms

To explore the continuous relationship between the selected PANSS N-items and cognition in the entire clinical sample, we performed three Pearson correlations between total negative symptom level (adding up all five selected N-items) and the cognitive composite score for baseline, 1-year follow-up and for the change in cognitive composite score over one year. Change scores for both total negative symptoms and the cognitive composite were calculated by subtracting baseline values from 1-year follow-up.

3. Results

3.1. Demographic and clinical variables

Clinical and demographic statistics are presented in Table 1. There were significant differences between the four negative symptom groups for IQ, depressive symptoms and gender. There was also a significant difference for diagnoses, where psychosis NOS was more frequent in the MNS-group (Table 1).

The negative symptoms that were most frequently sustained in the SNS group were emotional withdrawal (N2) with 12/26 (46%) and passive apathetic social withdrawal (N4) 11/26 (42%). Three (12%) patients in the SNS group had different PANSS negative items ≥ 4 at baseline and follow-up. In the TNS group, the most frequent symptoms were blunted affect (N1) 11/23 (48%) and passive apathetic social withdrawal (N4) 10/23 (43%).

3.2. Analysis of baseline differences in cognition

The omnibus MANOVA with negative symptom group as the independent variable revealed a significant and large overall effect on cognitive performance in the four cognitive domains (Wilks' Lambda = 0.52, $F_{4, 169} = 7.50$, $p < .001$, $\eta^2 = 0.15$). This main effect of negative symptom group remained significant in six follow-up MANCOVAs correcting for age (Wilks' Lambda = 0.51, $F_{4, 168} = 7.70$, $p < .001$, $\eta^2 = 0.15$), gender (Wilks' Lambda = 0.53, $F_{4, 168} = 7.28$, $p < .001$, $\eta^2 = 0.15$), positive symptoms (Wilks' Lambda = 0.72, $F_{3, 82} = 2.31$, $p = .009$, $\eta^2 = 0.10$), depression (Wilks' Lambda = 0.72, $F_{3, 82} = 2.32$, $p = .008$, $\eta^2 = 0.10$), antipsychotic medication (Wilks' Lambda = 0.74, $F_{3, 82} = 2.13$, $p = .016$, $\eta^2 = 0.10$) and IQ (Wilks' Lambda = 0.68, $F_{4, 166} = 4.18$, $p < .001$, $\eta^2 = 0.09$).

The one-way ANOVAs investigating the effect of negative symptom group on the four cognitive domains at baseline is displayed in Fig. 1. No significant differences were detected between the NNS group and healthy controls on any domain. All other negative symptom groups performed poorer than healthy controls on all domains, except the MNS group for *Verbal learning and memory* ($M = 0.37$, 95% CI [−0.98, 0.24], $d = 0.40$, $p = .61$). The SNS group was outperformed by the NNS group on *Processing speed* ($M = 1.44$, 95% CI [0.32, 2.56], $d = 1.0$, $p = .003$) and *Executive functions* ($M = 1.27$, 95% CI [0.39, 2.14], $d = 1.2$, $p = .001$), and on *Verbal learning and memory* by the MNS ($M = 1.24$, 95% CI [0.47, 2.00], $d = 1.1$, $p < .001$) and TNS ($M = 0.88$, 95% CI [0.09, 1.67], $d = 0.7$, $p = .02$) groups.

The ANOVA performed for negative symptom group effect on the cognitive composite score was significant ($F_{4, 169} = 1.03$, $p > .001$). The post hoc analysis showed that all negative symptom groups except the NNS performed significantly poorer than the healthy controls. Additionally, the SNS group performed significantly poorer than the NNS ($M = 1.07$, 95% CI [0.31, 1.84], $d = 1.2$, $p = .001$) and MNS ($M = 0.76$, 95% CI [0.15, 1.36], $d = 0.9$, $p = .005$) groups. The difference between the SNS and TNS group was trend level significant ($M = 0.62$, 95% CI [0.00, 1.25], $d = 0.61$, $p = .051$) (Fig. 2).

3.3. Analysis of cognitive course

The MANOVA which was performed to investigate whether negative symptom group was associated with differences in cognitive course

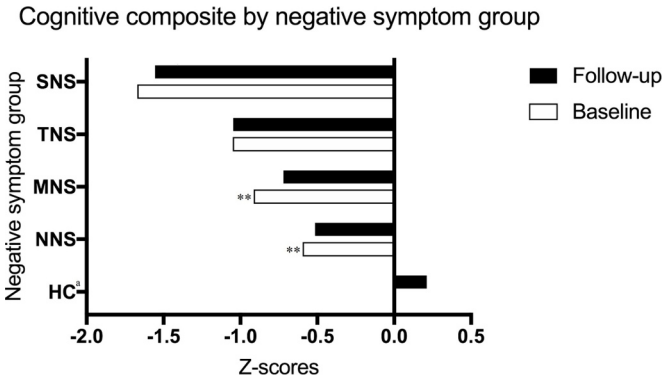

Fig. 2. *Note:* NS = Negative Symptoms; No, Mild, Transitory, Sustained. Statistical results are not presented for follow-up data, but are shown to illustrate change over time.

**Different from SNS ($p < .01$).

[a]HC = Healthy controls outperformed all groups ($p < .01$) except NNS ($p = .12$).

in the four cognitive domains was non-significant (Wilks' Lambda = 0.91, $F_{4, 169} = 1.03$, $p = .42$, $\eta^2 = 0.02$), indicating no difference in cognitive course between the negative symptom groups over the one year follow-up period.

3.4. Analysis of the continuous relationship between cognition and negative symptoms

The analyses of the continuous relationship between negative symptoms and cognition revealed strong and significant negative correlations between the cognitive composite score and the total level of negative symptoms both at baseline ($r = -0.36$, $p = .001$) and follow-up ($r = -0.32$, $p = .003$). There was no significant correlation between change in negative symptoms and change in the cognitive composite score ($r = -0.17$, $p = .12$).

4. Discussion

In a sample of 87 participants with a broad schizophrenia spectrum disorder, we applied a stratification method to investigate different levels of negative symptoms over a one-year follow-up period. Our primary objective was to investigate the hypothesis that level of negative symptoms over one year early in the course of illness is associated with cognitive function. Our findings support the main hypothesis by showing an effect of negative symptom group on overall cognition, which could not be explained by age, gender, positive symptoms, antipsychotic medication or IQ. On the domain level, participants in the sustained negative symptom group were outperformed by participants in the group with no negative symptoms on executive functions and processing speed, and by those with mild and transitory negative symptoms on verbal learning and memory. A gradient between negative symptom severity over one year and cognitive functioning was observed for general cognitive ability represented by the cognitive composite score. The sustained group was most severely impaired, and significantly more impaired than the no and mild negative symptom groups, with the difference from the transitory group trending towards significance. Only the group with no negative symptoms was not significantly different from healthy controls on this measure.

Our second aim was to investigate whether levels of negative symptoms early in the course of illness was related to the course of cognitive functioning over 1 year. There was no between-group difference in cognitive course over the follow-up period. This is in keeping with the general finding that the cognitive course is stable on the group level in first-episode psychosis (Mesholam-Gately et al., 2009). A study which further divided a schizophrenia sample into clinical subgroups based on age, age at onset, baseline cognitive impairment, worsening or improvement of clinical symptoms and occurrence of incident tardive dyskinesia over short (1.6 years) and medium (5 years) follow-up periods, also found no significant difference in cognitive course (Heaton et al., 2001). With regard to the continuous relationship between cognition and negative symptoms, changes in negative symptoms were unrelated to changes on the cognitive composite score in our study sample.

Previous research has reported a specific relationship between apathy and executive functions (Faerden et al., 2009; Konstantakopoulos et al., 2011). The largest effect size in the current study was in the executive functioning domain between the sustained and no negative symptom groups, and the most frequently sustained N-items were N2 (emotional withdrawal) and N4 (passive apathetic social withdrawal), which are both related to apathy (Faerden et al., 2008). Further, our sustained group resembles the persistent negative symptom subgroup as operationalized by Galderisi et al. (2013). They found slightly lower mean values on five of their six cognitive tests for a persistent negative symptom subgroup as compared to a control group with only baseline negative symptoms. Our transitory group resembles their control group with moderate to above symptom severity that was not sustained through one year. Comparing the sustained and transitory groups in our study, we find similar impairments compared to healthy controls, and a small difference between the two groups which is not significant, except for verbal learning and memory. Thus, differences in cognition appear more clearly when participants with sustained negative symptoms are compared to those with mild or no negative symptoms over one year.

Verbal learning and memory, particularly immediate verbal memory, is reported to be among the most impaired cognitive domains in FEP (Mesholam-Gately et al., 2009). Our finding that this domain was impaired in the sustained group relative to all other groups, except the group with no negative symptoms, seems counter-intuitive. This could be due to the relatively small size of the group with no negative symptoms, as this increases the likelihood of Type II error.

For the purpose of studying negative symptoms as a target for treatment, researchers have stressed the need to identify primary negative symptoms, which are not confounded by depression, positive symptoms or extrapyramidal side effects (Buchanan, 2006; Mucci et al., 2017). The aim of the current study was not to attribute changes to a specific cause, but rather to investigate how levels of negative symptoms over time were associated with cognition. Moreover, depression did not influence our findings, and there were no significant differences in positive symptoms between the negative symptom groups.

Furthermore, as our aim was to investigate how cognitive functioning is related to the entire spectrum of negative symptom severity, it was important to include the whole sample. Our findings suggest that the association between cognition and negative symptoms, which has been found to be modest in cross-sectional studies, may be stronger when symptoms are evaluated over time. This is important because, although more stable than positive symptoms, negative symptoms also fluctuate over time (Austin et al., 2015), and more so for a subset of patients (Ventura et al., 2015). Therefore, we note that our two groups, defined by their stability of either high (SNS) or absent (NNS) levels of negative symptoms, represent clear opposites in terms of cognitive functioning. It has been argued that patients with persistent negative symptoms form a separate disease entity within schizophrenia, and not simply a more severe form of the same illness (Kirkpatrick et al., 2001). This is further underlined by the fact that these patients do not have more positive symptoms. Kaiser et al. (2011) argue against this view, pointing out that severity could be understood along several symptom dimensions, and not one severity continuum. They also review evidence supporting a view of negative symptoms as continuous, transdiagnostic and present in the healthy population (Kaiser et al., 2011). Our results seem to support the notion that negative symptom scores are relevant in relation to cognition across the entire scale. However, the relationship between cognition and negative symptoms is most prominent when comparing the extremes, where participants with sustained negative symptoms are cognitively impaired as a group, while the group with no negative symptoms does not statistically differ from the healthy controls.

Investigating the relationship between cognitive and negative symptoms is important for several reasons. First, it is well established that these symptoms do not respond well to currently developed treatments (Owen et al., 2016). Furthermore, these symptoms account for significant amounts of variation in functional outcome. Finally, the search for underlying neural and genetic mechanisms of psychotic disorders could benefit from identification of meaningful subgroups.

Although the current findings do not point to causality or etiology, they do inspire questions. Studies investigating the relationship between motivational factors and cognitive test performance have found significant positive correlations, which the authors interpret to mean that cognitive symptoms in schizophrenia are partly secondary to amotivation (Fervaha et al., 2014; Moritz et al., 2017). In an editorial comment to Fervaha et al. (2014), Keefe (2014) offers a different interpretation of the results. He questions the direction of causality proposed by the authors and cites evidence from basic animal and clinical

neuroscience which suggests that motivational functioning is integrated with both cognitive and psychomotor functioning in effortful decision making (Keefe, 2014). Our results did not show an association between changes in negative symptoms and the cognitive composite score, but this does not mean that motivational factors can or should be discounted.

4.1. Strengths and limitations

The strengths of the study include the use of a longitudinal, prospective design and the inclusion of a healthy control group matched on age and gender. The study also includes data from a relatively broad neuropsychological test battery with assessments at both time points.

There are, however, also some limitations that warrant mentioning. Although the first year of treatment is a very important period, it is a relatively short follow-up period. Different patterns of negative symptoms might emerge over longer time periods.

Furthermore, as symptom levels were only evaluated at two time points, our knowledge of how they may have fluctuated over the follow-up period is limited. Finally, our sample size is relatively small for analyzing differences in subgroups, particularly for the smallest group (NNS), which could increase likelihood of Type II error.

4.2. Conclusions

Negative symptoms vary both in degree and stability early in the course of treatment. Studies exploring the relationship between course of negative symptoms and cognitive function in a longitudinal design are few and generally focus on patients above specified levels of symptoms. By using 1-year follow-up data we show that there is a dose-response relationship between the severity in negative symptoms and cognitive functioning exploring all symptom levels over a 1-year period in a FEP sample. Participants with sustained moderate to high levels of negative symptoms over one year were significantly more impaired on the overall cognitive composite compared with those having no or only mild negative symptoms, with large effect sizes. Significant between-group differences were detected in the domains of executive functions, processing speed and memory and learning. Changes in negative symptoms were not associated with changes on the cognitive composite score. This suggests a possible trait-like quality of the association between negative symptoms over time and level of cognitive functioning. This association was robust and could not be explained by confounding effects of age, gender, positive symptoms, depression, antipsychotic medication or IQ.

Given the large differences in cognitive functioning, especially between the groups with sustained and no negative symptoms, it is important for clinicians to notice the early course of negative symptoms. In clinical settings where resources for cognitive assessments might be limited, the early course of negative symptoms gives potentially important information about cognitive resourcefulness or impairment depending on whether symptoms are completely absent or prominent and sustained.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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