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Working memory and learning impairments in deficit and non-deficit schizophrenia, and their associations with negative symptoms: A mediation analysis Authors

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Abstract

The aim of the study: To explore differences in working memory and learning between individuals with deficit schizophrenia (DS), non-deficit schizophrenia (NDS), and healthy controls (HC), and to assess whether working memory mediates the relationship between negative symptoms and learning in schizophrenia.

Material and methods: Twenty-nine DS patients, 45 NDS patients, and 39 HC were assessed. Working memory and learning were measured using the Letter-Number Span Test, Spatial Span Subtest, Hopkins Verbal Learning Test – Revised, and Brief Visuospatial Memory Test – Revised. Psychopathological symptoms were evaluated with the Positive and Negative Syndrome Scale, Brief Negative Symptom Scale, and Self-evaluation of Negative Symptoms.

Results: DS patients scored lower on all working memory and learning measures compared with their NDS counterparts and HC. Despite similar learning profiles, DS patients exhibited significantly reduced performance. The mediation model showed good fit indices, suggesting that verbal and visual working memory significantly mediate the relationships between negative symptoms and both verbal and visual learning in patients with schizophrenia.

Discussion: Patients with DS exhibit impairments in both verbal and visual working memory and learning. Nonetheless, the capacity for new learning is preserved, albeit to a reduced degree. These findings suggest working memory's role as a neurocognitive mechanism linking negative symptoms to learning deficits in schizophrenia.

Conclusions: Cognitive remediation programs for schizophrenia should incorporate tasks aimed at enhancing working memory.

deficit schizophrenia; working memory; learning; cognitive impairments; negative symptoms

1. INTRODUCTION

Schizophrenia is now recognised as a complex neurodevelopmental disorder [1] with significant cognitive impairment, leading to functional impairment in various domains of life [2]. Alongside deficits in attention, executive func-

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tion, and language, its clinical presentation includes memory impairment [3-5]. In line with the multidimensional approach and in order to sort out existing variance in psychopathological symptomatology, subgroups of schizophrenia with distinct genetic and neurobiological predispositions have been proposed [6,7]. Among them is the deficit type, with dominant primary and persistent negative symptoms [8]. Research to date has shed light on the nature of cognitive impairment in this variant of schizophrenia [9,10].

The deficit subtype was first presented by Carpenter et al. [11], who described its characteristic primary and persistent deficit symptoms, such as blunted affect, reduced range of emotional responses, poverty of speech with reduced cognitive curiosity, reduced sense of purpose, and social withdrawal. Longitudinal studies show these symptoms to persist in patients over many years [12,13]. The deficit type is distinguished from its non-deficit counterpart by risk factors [14,15], family history [16], course of illness [12,17] and response to pharmacological treatment [18]. In addition, more severe cognitive impairment [9,10] and greater structural and functional brain abnormalities are suggested to be present in the former subtype [19-21].

In their meta-analysis, Bora et al. [9] suggest that individuals with the deficit type exhibit greater difficulties in both verbal and visual memory compared to those without the deficit. However, their findings are inconsistent with those of a previous meta-analysis by Cohen et al. [10], who indicated that patients with both subtypes manifested similar performance in verbal, visual and working memory. In their original study, the authors demonstrated that there were no differences between the two clinical groups in terms of verbal and visual memory. Given the paucity of detailed analyses concerning intergroup differences in verbal and non-verbal learning and working memory in the above meta-analyses, we decided to consider and analyze individual studies. A number of these indicated that individuals with deficit schizophrenia (DS) exhibited greater impairment in verbal memory [22-24], verbal learning [25-27] and working memory [22,27-32], compared with the non-deficit schizophrenia (NDS) patients. Conversely, other reports showed DS patients to have greater problems in visual memory or visual learning tasks [28,33,34]. Our previous research also demonstrates that DS patients manifest greater difficulties in working memory and learning, as well as other cognitive functions [35]. However, the existing body of evidence includes contradictory results, with some studies failing to demonstrate significant differences between the two patient groups in verbal, visual, and working memory [36-39]. As none of the aforementioned research considered (verbal or non-verbal) learning curves, focusing rather on general measures only, the knowledge about these processes in DS is still incomplete.

Attempts to explain the close links demonstrated between working memory and learning have been made in various theoretical models [40], with Baddeley's working memory model [41] as the most popular one. The model includes three components: the central executive system, phonological loop and visuospatial sketchpad, conceptualising working memory and temporary stores of information as a system of fluid cognitive abilities that cannot be modified by learning. They, however, affect the learning process and the subsequent storage of information in long-term memory, which is a system of crystallised, accumulated knowledge [42]. The phonological loop has been found to be more closely associated with verbal, and the visuospatial sketchpad with non-verbal storage, as evidenced by studies conducted on individuals with brain damage [43] and healthy individuals [44,45]. The mechanism underpinning the relationship between working and long-term memory in schizophrenia has been suggested to involve a shared information encoding system, grounded in both cognitive and neural processes [46-48]. In addition, a recent meta-analysis has demonstrated that memory and learning deficits in schizophrenia are linked to reduced hippocampal volume [49].

There is compelling evidence indicating an association between psychopathological symptomatology, particularly positive, negative and disorganisation symptoms, and cognitive impairment, primarily in executive function and verbal fluency, in individuals diagnosed with schizophrenia [50-52]. Doughty and Done [3] also point out links of negative symptoms with memory deficits in schizophrenia. However, there is a relative paucity of data pertaining par-

ticularly to memory and learning in DS. To date, negative symptoms in DS have been associated with working memory [30,32] and verbal learning [30]. Furthermore, Bryson et al. [34] demonstrated an association of deficit symptoms with an overall measure of verbal learning, while Chen et al. [39] showed links between commonly reported psychopathological symptoms and verbal memory. The current state of debate regarding the relationship between psychopathological symptoms and cognitive functioning in schizophrenia [53] highlights the need for further research in this area, particularly in the context of DS.

There are grounds to believe that links between psychopathological presentation of schizophrenia and cognitive functions, such as working memory and learning, may be more complex. Studies to date suggest that processing speed and cognitive flexibility play a mediating role between negative symptoms, working memory [54] and semantic fluency, which is a measure of the mental lexicon – i.e., the storehouse of long-term memory [55,56]. Should such mediating effects be confirmed, it would be advisable for therapeutic efforts concerning enhancing learning processes in individuals with schizophrenia to target working memory, alongside mere improvement of psychopathological symptoms.

Existing neuropsychological literature has contributed to the enhancement of knowledge concerning cognitive impairment in individuals diagnosed with DS. Nevertheless, in the absence of consensus regarding both theoretical inquiries and practical implications, the nature of memory impairment in DS patients remains to be fully elucidated. This study was designed to fill this gap in the literature regarding the specificity of working memory and learning deficits in schizophrenia and their association with negative symptoms. Initially, our aim was to compare verbal and non-verbal working memory and learning between individuals with deficit and non-deficit schizophrenia and healthy controls. Our main focus, however, was to test a mediation model to ascertain whether the relationship between negative symptoms and learning is mediated by working memory in people with schizophrenia.

2. MATERIAL AND METHODS

2.1. Participants

Seventy-four outpatients diagnosed with schizophrenia according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [57] and the Mini-International Neuropsychiatric Interview, 3rd Edition (MINI) [58] were recruited from the Department of Psychiatry at xxxx University and affiliated psychiatric clinics in xxxx. Thirty-nine healthy controls (HC), without any psychiatric or neurological disorders, recruited via advertisements among university staff and students, served as the comparison group.

Based on Kirkpatrick et al.'s criteria for the deficit syndrome [59], clinical participants were divided into two subgroups: deficit (n = 29) and non-deficit schizophrenia (n = 45). Although the Schedule for the Deficit Syndrome (SDS) [60,61] was not administered, the deficit status was operationalised following Fervaha et al. [22] and Putnam and Harvey [25], by selecting five Positive and Negative Syndrome Scale (PANSS) items corresponding to the following SDS domains: Blunted affect (N1), Emotional withdrawal (N2), Lack of spontaneity and fluency of conversation (N6), Disturbance of volition (G13), Passivity/apathetic social withdrawal (N4). Patients scoring ≥ 4 on any of these items were classified as having DS. All clinical assessments were conducted by board-certified psychiatrists using semi-structured interviews and available medical records.

Inclusion criteria were: ICD-10 diagnosis of schizophrenia, illness duration > 10 years, age 30–50 years, and written informed consent. Exclusion criteria included comorbid psychiatric disorders (other than schizophrenia), neurological or severe medical conditions affecting cognition, substance use disorders, and a history of head injury with loss of consciousness. All participants provided written informed consent, and the study was approved by the Local Ethics Committee.

2.2. Neuropsychological assessment

Four tests from the Polish adaptation of the MATRICS Consensus Cognitive Battery were

administered to assess working memory and learning abilities [62,63].

The Letter-Number Span Test (LNST) was used to assess verbal working memory. Participants were verbally presented with randomized sequences of letters and digits and instructed to recall and manipulate them. Performance was scored as the total number of correctly recalled sequences, in line with Nuechterlein et al. [62].

The Spatial Span Subtest of the Wechsler Memory Scale – Revised (SSS) was used to measure visual working memory. Participants reproduced sequences of tapped blocks in forward and backward order. The score for backward trials was analysed as recommended by Cornoldi and Mammarella [64].

Three learning trials of the Hopkins Verbal Learning Test – Revised (HVLT-R) were used to measure verbal learning. Each trial involved presentation of the same 12-word list, and subsequent recall of as many items as possible. Learning outcomes included total recall across all trials and trial-by-trial recall, according to Shapiro et al. [65].

The Brief Visuospatial Memory Test – Revised (BVMT-R) across three trials was used to test visual learning. On each trial, participants studied a 2 x 3 array of designs for 10 seconds, then reproduced them from memory. Scores comprised the number of correctly recalled and correctly located designs per trial, as well as the total learning score, following Benedict et al. [66].

2.3. Premorbid intellectual functioning

Indirect premorbid intellectual functioning (IQ) was estimated using the Vocabulary and Picture Completion subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) [67], validated as indirect measures thereof in schizophrenia [68]. The Vocabulary subtest indexed crystallized intelligence, and the Picture Completion subtest indexed fluid intelligence, per Sumiyoshi et al. [69]. For both subtests, raw scores were calculated as the sum of correct responses; additionally, completion time was recorded for Picture Completion in accordance with the WAIS-R manual.

2.4. Clinical assessment

Psychopathological symptoms were assessed with the Polish adaptation of the Positive and Negative Syndrome Scale (PANSS) [70,71]. Factor scores were computed using Shafer and Dazzi's five-factor model, including: positive, negative, disorganisation, affective, and arousal symptoms [72]. Negative symptoms were further evaluated using the Polish adaptations of the Brief Negative Symptom Scale (BNSS) [73,74] and the Self-evaluation of Negative Symptoms (SNS) [75,76]. Overall functioning was measured with the Global Assessment of Functioning (GAF) scale [77].

2.5. Statistical analysis

All analyses were performed in IBM SPSS Statistics version 29 and AMOS version 9. Continuous variables are reported as mean (M) ± standard deviation (SD). Normality was assessed with the Shapiro-Wilk test; skewness and kurtosis values between – 2 and +2 were deemed acceptable [78]. Years of education, age, indirect premorbid crystallized IQ (Vocabulary from WAIS-R), LNST, SSS, HVLT-R learning trials, GAF, chlorpromazine equivalents, and duration of illness approximated normality. In contrast, number of exacerbations, PANSS factor scores, indirect premorbid fluid IQ (Picture Completion from WAIS-R), BNSS and SNS scores, and total HVLT-R and BVMT-R scores deviated from normality and were log- or Box-Cox-transformed prior to analysis [79]. Student's t-tests compared clinical factors and psychopathology between DS and NDS groups. One-way analysis of variance (ANOVA) or a 3 x 3 mixed-design ANOVA (group x learning trial) with Bonferroni post hoc tests examined group differences in age, education, IQ, and cognitive measures. Effect sizes were calculated as Cohen's d, Cramér's V, or η^2 [80]. Based on literature linking gender [81], education [82], and IQ [83] to cognition in schizophrenia – and given the existing intergroup differences in these variables – we tested their suitability as covariates, following Maroof [84]. A two-way ANOVA (gender x group) showed no interaction, but years of education correlated significantly ($r > 0.30$) with

WAIS-R and cognitive test scores; gender did not. Thus, only education entered the ANCOVA model as a covariate [85].

To estimate the sensitivity analysis for ANOVA, G*Power software was used [86], indicating that an ANOVA with 113 participants across the three groups would be sensitive to effects of $\eta^2 = 0.12$ with 95% power ($p = 0.05$), thus suggesting that this study would not reliably detect effects smaller than $\eta^2 = 0.12$.

Associations among negative symptoms, working memory, and learning were examined using Pearson's correlations. Confirmatory factor analysis (CFA) and structural equation modeling (SEM) were conducted to model negative symptoms as a latent variable indicated by BNSS and SNS scores, thereby reducing measurement error and increasing power [87]. SEM specification followed Baron and Kenna [88]. Mediation prerequisites were tested via correlations, and the mediation model was evaluated in the combined schizophrenia sample with verbal working memory (LNST) and visual working memory (SSS) as mediators. Model fit was assessed using χ^2, RMSEA (< 0.07), SRMR (< 0.08), GFI, and CFI (> 0.95) [89]. Indirect, direct, and total effects were estimated with bias-corrected bootstrap (10,000 samples) and 95% confidence intervals [90]. Standardized path coefficients (β) are reported, and statistical significance was set at $\alpha = 0.05$ (two-tailed).

3. RESULTS

3.1. Demographic, psychological, and clinical characteristics

Table 1 presents the demographic, psychological, and clinical characteristics of all participants. Age did not differ significantly between groups. In contrast, sex distribution ($p = 0.011$), years of education ($p = 0.020$), and both indirect premorbid IQ: fluid (Picture Completion; $p < 0.001$) and crystallized (Vocabulary; $p < 0.001$) all differed significantly among the three groups.

Following the Holm-Bonferroni correction for multiple comparisons, DS patients showed significantly greater negative symptom severity and higher total PANSS scores compared with NDS patients (negative symptoms: $p < 0.001$; total PANSS: $p = 0.005$). They also scored higher on the BNSS and SNS (both $p < 0.001$). No significant differences were observed between DS and NDS patients in type of antipsychotic medication, chlorpromazine equivalents, illness duration, number of exacerbations, global functioning (GAF), or other PANSS symptom dimensions.

Table 1. Demographic, psychological, and clinical characteristics of all participants.

Variables / Groups	Deficit schizophrenia patients (DS) (n = 29)	Non-deficit schizophrenia patients (NDS) (n = 45)	Healthy controls (HC) (n = 39)	F / χ^2 / t	η^2 / V / d
Age: M (SD)	38.59 (6.17)	39.16 (7.21)	37.08 (7.94)	0.90[c]	0.02[f]
Years of education: M (SD)	12.66 (3.24)[j*]	13.53 (2.64)	14.59 (2.62)	4.06[c*]	0.00[f]
Sex, female / male: n (%)	7 (24.14) / 22 (75.86)	24 (53.33) / 21 (46.67)	23 (58.97) / 16 (41.03)	9.01[d*]	0.28[g]
Premorbid IQ in WAIS-R:					
Picture Completion: M (SD)	17.86 (7.60) / 20.52 (13.35)[b,i**,j***]	22.56 (6.13) / 29.53 (13.24)[b,k***]	29.62 (3.63) / 47.46 (10.34)[b]	43.27[c***]	0.44[f]
Vocabulary: M (SD)	33.97 (14.47)[i***,j***]	43.40 (10.18)[k***]	56.18 (6.55)	38.81[c***]	0.41[f]
Antipsychotic medications:					

Atypical: n (%)	20 (68.98)	29 (64.44)		2.09[c]	0.17[g]
Atypical and typical: n (%)	8 (27.57)	12 (26.67)			
Typical: n (%)	0 (0.00)	3 (6.67)			
No medications: n (%)	1 (3.45)	1 (2.22)			
Chlorpromazine equivalent (mg): M (SD)	695.86 (311.57)	644.04 (309.71)		0.70[e]	0.17[h]
Duration of illness: M (SD)	16.97 (5.72)	14.00 (5.14)		2.32[e]	0.55[h]
Exacerbation: M (SD)	5.69 (2.44) / 1.64 (0.48) [a]	6.49 (5.01) / 1.65 (0.64) [a]		-0.11[e]	-0.03[h]
Global functioning in GAF: M (SD)	50.93 (14.34)	58.40 (14.21)		-2.20[e]	-0.52[h]
Psychopathological symptoms in PANSS:					
Positive symptoms: M (SD)	7.38 (2.73) / 0.53 (0.01) [b]	8.07 (4.37) / 0.53 (0.01) [b]		0.00[e]	0.00[h]
Negative symptoms: M (SD)	22.24 (4.66) / 0.59 (0.00)[b]	13.80 (5.19) / 0.58 (0.00)[b]		6.35[e***]	1.53[h]
Disorganization: M (SD)	12.62 (3.48) / 0.54 (0.00)[b]	11.42 (3.98) / 0.53 (0.00)[b]		1.93[e]	0.46[h]
Affect: M (SD)	8.24 (3.45) / 0.53 (0.01) [b]	9.29 (3.53) / 0.53 (0.01) [b]		-1.68[e]	-0.40[h]
Resistance: M (SD)	4.34 (0.62) / 0.50 (0.00) [b]	4.89 (2.43) / 0.51 (0.01) [b]		-0.98[e]	-0.23[h]
Total score: M (SD)	56.83 (11.17) / 0.54 (0.00)[b]	49.33 (14.68) / 0.54 (0.00)[b]		3.08[e**]	0.73[h]
Negative symptoms in BNSS:					
Total score: M (SD)	47.09 (9.28) / 0.47 (0.09)[b]	20.07 (12.68) / 0.20 (0.13)[b]		9.88[e***]	2.35[h]
Negative symptoms in SNS:					
Total score: M (SD)	22.28 (7.38) / 0.75 (0.16)[b]	9.71 (6.89) / 0.43 (0.19) [b]		7.52[e***]	1.79[h]

Note. BNSS – Brief Negative Symptom Scale. GAF – Global Assessment of Functioning. PANSS – Positive and Negative Syndrome Scale. SNS – Self-evaluation of Negative Symptoms. WAIS-R – Wechsler Adult Intelligence Scale Revised Fourth Edition. aMean and standard deviation after logarithmic transformation. bMean and standard deviation after Box-Cox transformation. cOne-way analysis of variance F test. dChi-squared test. eStudent's t test. fEta squared effect size: small (0.01-0.059), medium (0.06-0.139), large (0.14-1.00). gCramer's V effect size: small (0.10-0.19), medium (0.20-0.59), large (0.60-1.00). hCohen's d effect size: small (0.20-0.49), medium (0.50-0.79), large (0.80 <). All p-values for ANOVA: iDS patients vs. NDS patients, jDS patients vs. HC participants, kNDS patients vs. HC participants. All p-values for Student's t test are after Holm-Bonferroni p-value correction. * p < 0.05. ** p < 0.01. *** p < 0.001.

3.2. Differences in working memory and learning

As shown in Table 2, significant group differences emerged for verbal working memory (LNST; $p < 0.001$), visual working memory (SSS; $p < 0.001$), verbal learning (HVLT-R total score; $p < 0.001$), and visual learning (BVMT-R total score; $p < 0.001$). Post hoc comparisons indicated that DS

patients scored lower than NDS patients on both verbal working memory (LNST; $p < 0.001$) and visual working memory (SSS; $p = 0.003$), as well as on verbal learning (HVLT-R total; $p = 0.006$) and visual learning (BVMT-R total; $p < 0.001$). Both patient groups scored lower than healthy controls (HC) on all measures ($p < 0.001$). After adjusting for years of education and indirect premorbid fluid and crystallized IQ, the only remaining significant differences between DS and NDS patients were in visual learning: BVMT-R total score ($p = 0.020$) and individual trials (Trial 1: $p = 0.017$; Trial 2: $p = 0.011$; and Trial 3: $p = 0.004$) (see Table S1 in Supplementary Materials).

Table 2. Comparison of working memory and learning between the three groups.

Variables / Groups	Deficit schizophrenia patients (DS) (n = 29)	Non-deficit schizophrenia patients (NDS) (n = 45)	Healthy controls (HC) (n = 39)	F	η^2
Verbal working memory in LNST: M (SD)	8.69 (3.95)^{b***,c***}	12.24 (3.53)^{d***}	15.87 (3.26)	34.32***	0.38
Visual working memory in SSS: M (SD)	5.48 (2.29)^{b**,c***}	7.16 (2.18)^{d***}	9.21 (1.74)	27.56***	0.33
Verbal learning – sum score in HVLT-R: M (SD)	17.69 (6.79) / 1.96 (1.36)^{a,b**,c***}	22.40 (5.75) / 2.89 (1.32)^{a,d***}	28.13 (3.48) / 4.30 (0.98)^{a}	31.65***	0.37
Visual learning – sum score in BVMT-R: M (SD)	12.28 (8.45) / 1.22 (1.39)^{a,b***,c***}	20.31 (7.47) / 2.54 (1.50)^{a,d***}	30.00 (4.93)/ 4.92 (1.33)^{a}	61.28***	0.53

Note. BVMT-R – Brief Visuospatial Memory Test – Revised. HVLT-R – Hopkins Verbal Learning Test – Revised. LNST – Letter Number Span Test. SSS – Spatial Span Subtest. aMean and standard deviation after Box-Cox transformation. All p-values for Bonferroni post hoc for ANOVA: bDS patients vs. NDS patients. cDS patients vs. HC participants. dNDS patients vs. HC participants. ** p < 0.01. *** p < 0.001.

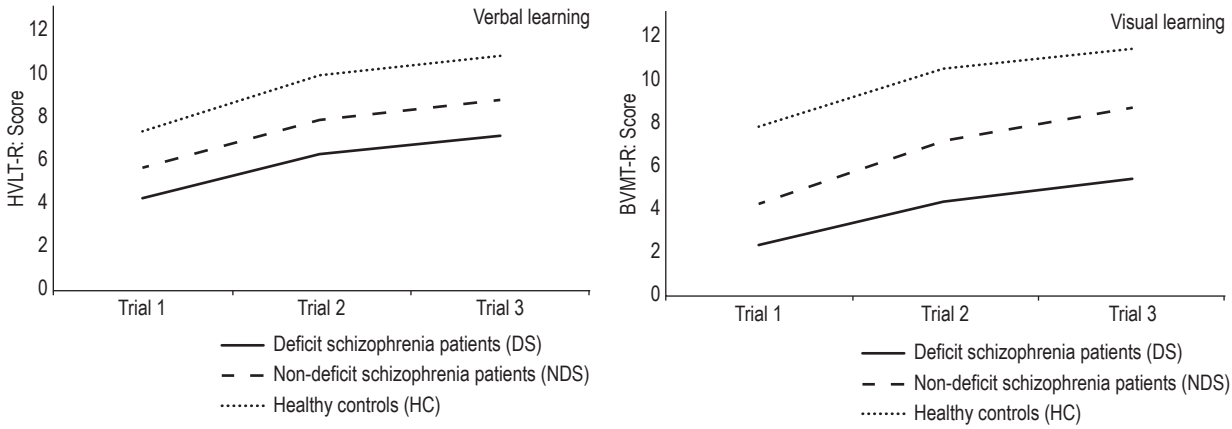

Figure 1. Verbal and visual learning across deficit schizophrenia (DS), non-deficit schizophrenia (NDS), and healthy controls (HC).
Note. BVMT-R – Brief Visuospatial Memory Test – Revised. HVLT-R – Hopkins Verbal Learning Test – Revised.

In addition, as shown in Figure 1, in the case of verbal learning, the main effects of group ($F = 31.87$; $p < 0.001$; $\eta^2 = 0.37$) and trial ($F = 245.23$; $p < 0.001$; $\eta^2 = 0.69$) were significant, but the group x trial interaction was not ($F = 1.15$; $p = 0.332$; $\eta^2 = 0.02$). Similar results emerged for visual learning: both main effects were significant (group: $F = 54.72$; $p < 0.001$; $\eta^2 = 0.50$; trial: $F = 168.16$; $p < 0.001$; $\eta^2 = 0.61$), whereas the interaction effect was not ($F = 2.32$; $p = 0.058$; $\eta^2 = 0.04$).

3.3. Mediation analysis

Correlations among negative symptoms, verbal and visual working memory, and verbal and visual learning in patients with schizophrenia are shown in the Supplementary Materials (Tables S2-S4). Table 3 and Figure 2 display the standardized effects of the mediation model, which tested whether verbal and visual working memory mediated the relationships between negative symptoms – modelled as a latent variable – and verbal and visual learning.

The mediation model was evaluated with a single latent variable, i.e., the negative symptoms, as indicated by BNSS ($\beta = 0.843$; $p < 0.001$) and SNS ($\beta = 0.889$; $p = 0.001$) scores. Negative symptoms exerted a significant total effect on verbal ($\beta = -0.380$; $p = 0.018$) and visual learning ($\beta = -0.493$; $p < 0.001$). The direct effect on verbal learning was non-significant ($\beta = -0.103$; $p = 0.450$), indicating full mediation by working memory, whereas the direct effect on visual learning remained significant ($\beta = -0.286$; $p = 0.020$), suggesting partial mediation. Verbal working memory significantly predicted verbal ($p < 0.001$) but not visual learning ($p = 0.136$), while visual working memory significantly predicted visual ($p = 0.007$) but not verbal learning ($p = 0.179$). Altogether, the model accounted for 41 % of the variance in both verbal and visual learning ($R2 = 0.41$ for each). Model fit was acceptable: $\chi^2 = 3.61$; $p = 0.307$; RMSEA = 0.053 (90% CI: 0.000-0.211; $p = 0.386$); SRMR = 0.018; GFI = 0.984; CFI = 0.997.

Table 3. Standardized effects for model of mediation between negative symptoms and learning via working memory in participants with schizophrenia.

	Total effect				Direct effect				Indirect effect			
	E	SE	95% CI	p	E	SE	95% CI	p	E	SE	95% CI	p
Model 1: Standardized effects for mediation												
Negative symptoms to verbal learning	-0.380	0.134	-0.594 to – 0.061	0.018	-0.103	0.131	-0.351 to 0.150	0.450	-0.278	0.088	-0.492 to – 0.132	0.001
Negative symptoms to visual learning	-0.493	0.112	-0.681 to – 0.247	<0.001	-0.286	0.120	-0.521 to – 0.047	0.020	-0.207	0.070	-0.376 to – 0.091	0.001

Note. CI – Confidence interval. E – Estimate. SE – Standard error.

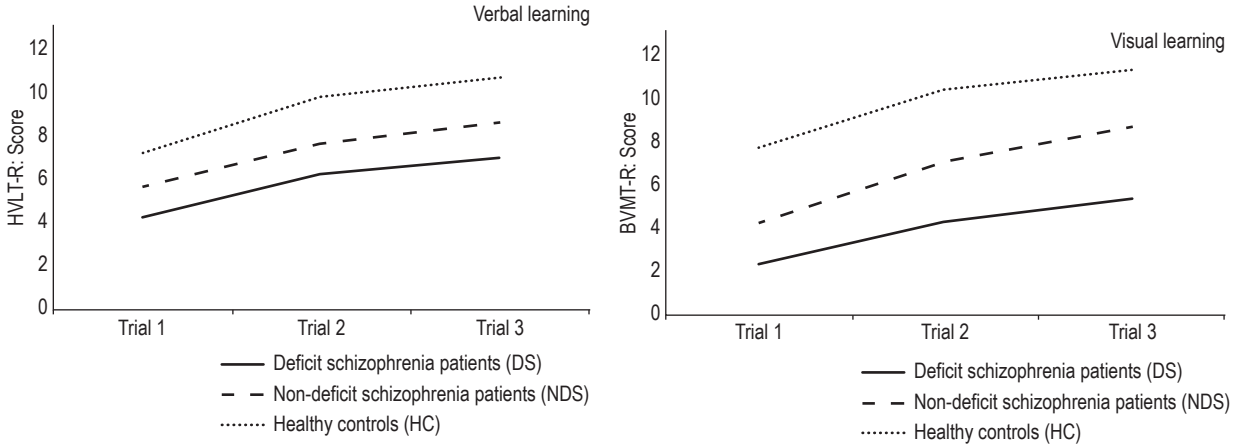

Figure 2. The mediation model showed verbal and visual working memory as mediators of the relationships between negative symptoms, and verbal and visual learning in schizophrenia patients.

Note. a1 path – Negative symptoms predicting verbal working memory. a2 path – Negative symptoms predicting visual working memory. b1 path – Verbal working memory predicting verbal learning. b2 path – Verbal working memory predicting visual learning. b3 path – Visual working memory predicting verbal learning. b4 path – Visual working memory predicting visual learning. c1 path and c2 path – Total effects. c'1 path and c'2 path – Direct effects. BNSS – Brief Negative Symptom Scale. BVMT-R – Brief Visuospatial Memory Test – Revised. e – Residual error variance. HVLT-R – Hopkins Verbal Learning Test – Revised. LNST – Letter Number Span Test. r – Item error variance. SNS – Self-evaluation of Negative Symptoms. SSS – Spatial Span Subtest.

4. DISCUSSION

This study sought to characterise working memory and learning in individuals with DS and NDS. Our results indicate that patients with the deficit subtype demonstrate greater impairments in both verbal and visual working memory as compared to those without primary negative symptoms. Although both clinical groups retain the capacity to learn new verbal and visual material, performance is markedly poorer in the deficit subtype. Notably, this is the first study to show that working memory mediates the relationship between negative symptoms and learning, with important clinical implications.

All patients with schizophrenia exhibited deficits in verbal and visual working memory, but these were more pronounced in the deficit group. This aligns with Bora et al. [9] and several other studies using tasks that heavily tax executive processes [22,27-32], but contrasts with others that employ simpler span tests [36-39]. Such differences may be accounted for by methodological inconsistencies, especially concerning working memory measures. In this study, we used the LNST, which significantly burdens the central executive system, requiring not only maintenance in memory of varied verbal stimuli (i.e., numbers and letters) but also arranging them in increasing order. Other studies have primarily relied on the use of the Digit Span, involving simple forward and backward recall of single-type stimuli (digits), and thus placing a relatively lesser strain on working memory. Consequently, they may be less sensitive to detecting deficits in patients with DS. In contrast, even though less research has been devoted to visual working memory, the emerging findings are more consistent. These studies, similarly to ours, are based on the use of the SSS, which, according to Baddeley [41], requires maintenance and manipulation of block-position sequences.

Profile analysis of individual learning trials in both applied tests demonstrated specific learning impairments in schizophrenia patients. To our knowledge, this is the first such analysis in people with DS. According to our observations, DS patients have a preserved mechanism underlying acquisition of new knowledge, both verbal and visual, but its efficiency is more reduced compared to their NDS counterparts. Previous studies considering total scores of learning trials, both verbal [22,25-27,34] and non-verbal [33], showed clearly reduced performance in patients with DS, which remains consistent with our study. This, in turn, means that schizophrenia with or without primary deficit symptoms is linked with decreased ability to acquire knowledge of various types, but does not eliminate the underlying cognitive mechanism of new learning. Neuroanatomical alterations – such as reduced hippocampal and prefrontal volumes and disrupted connectivity between key memory regions – likely underlie these deficits [49,91,92].

After adjusting for years of education (as a proxy for cognitive reserve) and indirect premorbid crystallized and fluid IQ, differences between deficit and non-deficit groups in working memory and verbal learning were no longer significant, whereas impairments in visual learning persisted for both individual trials and total BVMT-R scores. These results suggest that visual learning deficits may constitute a specific cognitive hallmark of DS, relatively independent of cognitive reserve and premorbid ability. Indeed, DS is characterised by enduring negative symptoms and a stable illness course [8], and such selective cognitive vulnerabilities have been reported previously [9,10,93].

Our primary objective was to identify factors contributing to impaired acquisition of new information in schizophrenia. Given the modest size of the deficit subgroup and heterogeneous correlational findings within each subtype, we conducted a comprehensive analysis across the entire schizophrenia cohort. Structural equation modelling with a latent variable for negative symptoms (indicated by BNSS and SNS scores) and verbal and visuospatial working memory as mediators demonstrated that working memory impairment serves as a neurocognitive mechanism linking negative symptoms to learning disruption. According to the model, and much in line with Baddeley's theoretical frameworks [41], verbal memory deficits play an important predictive role for verbal learning, and likewise, visual memory deficits play such a role for visual learning. Our findings are thus generally consistent with the meta-analytic reports of Doughty and Done [3] and several more recent studies

[30,32] linking negative symptoms, memory and learning in schizophrenia.

What is more, our results align with the ongoing search for the neurocognitive mechanisms linking psychopathological symptoms of schizophrenia with cognitive impairment. Several reports [54-56] have identified processing speed and cognitive flexibility as such potential mechanisms. In contrast, our study suggests that it might rather be working memory that could serve as an intermediary, but in different ways, depending on the type of processed information (verbal vs. visual encoding). It is precisely the manner of information encoding and neuronal activity that are postulated as shared mechanisms explaining the relationship between working and long-term memory in schizophrenia [46-48].

Our research makes a substantial contribution to the ongoing debate regarding neurocognitive mechanisms in schizophrenia. By highlighting working memory as a mediator of the impact of negative symptoms on learning, we underscore the potential value of targeted cognitive remediation. Interventions designed to enhance working memory – particularly those incorporating ecologically valid tasks and technologies such as virtual reality – may yield meaningful improvements in learning and everyday functioning [94-96].

Several limitations warrant consideration. First, we used a PANSS-based proxy to classify DS rather than the gold-standard SDS [61], and although consistent with Kirkpatrick et al. [59], the validity of this approach has yet to be formally tested. Second, the relatively small sample of DS patients limited our ability to conduct subgroup-specific SEM analyses. Of note, we still managed to analyze the complex links between deficit symptoms and learning as mediated by two significant factors for the entire clinical sample. Third, despite adjusting for gender, education, and indirect premorbid IQ via ANCOVA, residual confounding cannot be entirely excluded. Finally, restricting enrolment to patients with illness duration of >10 years enhances group homogeneity but limits generalisability to early-stage or first-episode schizophrenia. Future studies should replicate these mediation findings in larger, more diverse samples, validate alternative classification methods, and evaluate the efficacy of targeted working memory interventions in randomised controlled trials.

5. CONCLUSIONS

The present study demonstrated that individuals with DS exhibit greater impairments in both verbal and visual working memory and learning than those with NDS. We also identified working memory as a mechanism mediating the relationship between negative symptoms and learning. Greater negative symptom severity and poorer verbal working memory explain difficulties in acquiring verbal information, whereas greater negative symptom severity and visual working memory impairments contribute to difficulties consolidating visual information. Cognitive remediation programs should prioritise tasks enhancing both verbal and visual working memory to improve learning and everyday functioning in schizophrenia and support functional recovery across daily life activities.

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Data availability
The dataset generated and analyzed in this study may be available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Pomeranian Medical University in Szczecin (KB-0012/49/17 from 27 March 2017). All participants signed written consent to participate in the study.

Competing interests
The authors declare no competing interests.

Working memory and learning impairments in deficit and non-deficit schizophrenia, and their associations with negative symptoms: A mediation analysis
Supplementary Materials

Table S1. Comparison of working memory and learning in three groups after adjusted for years of education and/or IQ.

Variables	Deficit schizophrenia patients (DS) M (SE)	Non-deficit schizophrenia patients (NDS) M (SE)	Healthy controls (HC) M (SE)	Pairwise comparisons	Adjusted group effect			Covariate years of education effect			Covariate crystallized IQ effect			Covariate fluid IQ effect		
				DS patients vs. NDS patients	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2
LNST	10.94 (0.63)	12.69 (0.44)	13.69 (0.58)	0.059	4.26	0.017	0.07	7.54	0.007	0.07	11.92	<0.001	0.10	1.94	0.166	0.02
SSS	6.72 (0.39)	7.49 (0.27)	7.90 (0.35)	0.281	2.13	0.123	0.04	-	-	-	2.01	0.159	0.02	15.25	<0.001	0.12
HVLT-R: sum score	2.59 (0.23)	3.04 (0.16)	3.66 (0.21)	0.316	4.45	0.014	0.08	8.20	0.005	0.07	1.66	0.201	0.02	5.21	0.025	0.05
HVLT-R: trial 1	5.00 (0.35)	5.92 (0.24)	6.53 (0.32)	0.082	4.22	0.017	0.07	1.85	0.176	0.02	1.38	0.244	0.01	3.98	0.049	0.04
HVLT-R: trial 2	7.29 (0.39)	8.03 (0.27)	9.03 (0.35)	0.304	4.34	0.015	0.08	10.68	0.001	0.09	4.78	0.031	0.04	0.86	0.356	0.01
HVLT-R: trial 3	8.37 (0.42)	9.09 (0.30)	9.63 (0.38)	0.454	1.90	0.155	0.03	6.95	0.010	0.06	4.74	0.032	0.04	3.09	0.081	0.03
BVMT-R: sum score	1.83 (0.28)	2.72 (0.19)	4.25 (0.25)	0.020	17.00	<0.001	0.24	5.90	0.017	0.05	0.68	0.412	0.01	15.40	<0.001	0.13
BVMT-R: trial 1	3.06 (0.45)	4.55 (0.32)	7.15 (0.41)	0.017	18.06	<0.001	0.25	3.74	0.056	0.03	3.30	0.072	0.03	14.57	<0.001	0.12
BVMT-R: trial 2	5.69 (0.53)	7.54 (0.37)	9.25 (0.48)	0.011	9.51	<0.001	0.15	8.62	0.004	0.08	0.01	0.920	0.00	9.51	0.003	0.08
BVMT-R: trial 3	7.10 (0.55)	9.20 (0.38)	9.82 (0.50)	0.004	6.46	0.002	0.11	3.95	0.049	0.04	1.95	0.165	0.02	8.80	0.004	0.08

Note. BVMT-R – Brief Visuospatial Memory Test – Revised. F – Analysis of covariance (ANCOVA). HVLT-R – Hopkins Verbal Learning Test – Revised. LNST – Letter Number Span Test. M – Mean. SE – Standard error. SSS – Spatial Span Subtest. η^2 – Eta squared effect size: small (0.01-0.059), medium (0.06-0.139), large (0.14-1.00).

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