Journal of Psychiatric Research 171 (2024) 75–83

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Revisiting delusion subtypes in schizophrenia based on their underlying structures

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ARTICLE INFO

Keywords:
Schizophrenia
Delusions
Factor analysis
Paranoia
Monothematic vs. Pan-thematic
Diagnosis

ABSTRACT

A clear understanding of the pathophysiology of schizophrenia and related spectrum disorders has been limited by clinical heterogeneity. We investigated whether relative severity and predominance of one or more delusion subtypes might yield clinically differentiable patient profiles. Patients (N = 286) with schizophrenia spectrum disorders (SSD) completed the 21-item Peters et al. Delusions Inventory (PDI-21). We performed factor analysis followed by k-means clustering to identify delusion factors and patient subtypes. Patients were further assessed via the Brief Psychiatric Rating Scale, Brief Negative Symptom Scale, Digit Symbol and Digit Substitution tasks, use of cannabis and tobacco, and stressful life events. The overall patient sample clustered into subtypes corresponding to Low-Delusion, Grandiose-Predominant, Paranoid-Predominant, and Pan-Delusion patients. Paranoid-Predominant and Pan-Delusion patients showed significantly higher burden of positive symptoms, while Low-Delusion patients showed the highest burden of negative symptoms. The Paranoia delusion factor score showed a positive association with Digit Symbol and Digit Substitution tasks in the overall sample, and the Paranoid-Predominant subtype exhibited the best performance on both tasks. Grandiose-Predominant patients showed significantly higher tobacco smoking severity than other subtypes, while Paranoid-Predominant patients were significantly more likely to have a lifetime diagnosis of Cannabis Use Disorder. We suggest that delusion self-report inventories such as the PDI-21 may be of utility in identifying sub-syndromes in SSD. From the current study, a Paranoid-Predominant form may be most distinctive, with features including less cognitive impairment and a stronger association with cannabis use.

1. Introduction

Delusions represent a hallmark symptom of schizophrenia spectrum disorders (SSD), yet pathways of delusion formation remain elusive. Difficulty in delineating these pathways is due in part to the heterogeneity of delusions (Coltheart et al., 2007). While basic research using animal models is essential for understanding neurobiological pathways, validating any "delusional" rodent or other animal model seems improbable. Advances in delusion mechanism and treatment research thus entail reducing clinical heterogeneity among patients. Past efforts to subdivide delusions have been based on the thematic content of delusions (e.g. persecutory, grandiose, guilt) or how the delusional contents are experienced (e.g. ideas of reference, thought insertion/-withdrawal). Such delusion 'subtyping' has been deployed since schizophrenia was first described (Bleuler and Brill, 1924; Kraepelin et al., 1919), and although effectively communicating patients' experiences, it has not satisfactorily aided diagnosis or treatment (Albus, 2012; Debowska et al., 1998; Taylor, 1972). Schizophrenia subtypes, e.g. paranoid schizophrenia, were thus excluded from the DSM-5 (Mattila et al., 2015). We posit that delusion-informed subtyping was not necessarily invalid as a strategy but lacked sufficient empiric basis in its implementation. Our goal is to reapproach delusions empirically from patient reports, identify their latent structures in SSD, and identify patient subtypes and corresponding clinical profiles.

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https://doi.org/10.1016/j.jpsychires.2023.12.025
Received 15 August 2023; Received in revised form 10 December 2023; Accepted 12 December 2023
Available online 14 January 2024
0022-3956/Published by Elsevier Ltd.

Clinicians assess delusions on interview or with standardized scales. In clinical practice, delusion-specific scales are rarely used (Aboraya et al., 2018; Alter et al., 2021). In research, common clinician-administered scales such as the Positive And Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) assess delusions according to global impressions, which may inadequately quantify subtype severity (Nicholson et al., 1995; White, 2005). The Brown Assessment of Beliefs scale and the Diagnostic Interview for Psychosis provide ratings of specific delusional motifs on 7 and 8 items, respectively (Castle et al., 2006; Keefe et al., 2004). These scales thus span a broader swath of delusions but still may not be sufficiently comprehensive for subtyping purposes.

Comparatively, patient self-report scales allow for detailed evaluation. One entirely delusion-focused self-report scale is the Peters et al. Delusions Inventory (PDI). The PDI captures a broad range of delusions with participants then rating their distress, preoccupation, and conviction levels of each belief (Peters et al., 1999). A 21-item version (PDI-21) was found to reliably cover the themes of the original PDI-40 (Peters et al., 2004). The PDI-21 has been used primarily to assess delusional ideation in the general population (Fonseca-Pedrero et al., 2012; Lopez-Ilundain et al., 2006; Peters et al., 1999, 2004; Verdoux et al., 1998), but also proposed as a screening tool for clinical psychosis (Preti et al., 2007) and used as a measure of delusion severity in research participants with schizophrenia (Tuominen et al., 2022).

Several studies have examined the latent structures of PDI in the general population, with two studies attempting confirmatory analyses in smaller SSD samples (Peters et al., 2004; Wang et al., 2017). The original authors sampled 444 healthy participants followed by 33 schizophrenia inpatients and proposed a one-factor solution based on principal component analysis of the PDI "yes/no" score (Peters et al., 2004). The PDI yes/no score (PDI Y/N) is the total number of endorsed delusions whereas the PDI grand total score (PDI-Total) summates distress, preoccupation, and conviction subscores to account for corresponding severity of endorsed items (Peters et al., 1999, 2004; Wang et al., 2017). Subsequent factor analyses proposed one-factor solutions (Fonseca-Pedrero et al., 2012; Jones and Fernyhough, 2007; Prochwicz and Gaweda, 2015), or up to 7-factor solutions, all in general populations (Lopez-Ilundain et al., 2006; Verdoux et al., 1998).

Wang et al. (2017) then conducted a study on the PDI that included 1655 healthy students and 192 patients with schizophrenia and performed exploratory + confirmatory factor analyses on both the yes/no score and grand total scores. The authors confirmed a one-factor model of the total score in the student sample but failed to confirm in the patient sample (Wang et al., 2017), potentially indicating a unique factor structure in the schizophrenia population.

We hypothesized that patients with SSD can be differentiated according to delusion severity subtypes and that these subtypes would differ in other clinical characteristics. The PDI-21 covers an appropriate breadth of delusions and appropriate depth via assessment of distress, preoccupation, and conviction (Peters et al., 2004; Sisti et al., 2012), and was thus the optimal scale for our efforts. Our SSD sample (N = 286) is the largest used to subtype clinical delusions empirically from self-report (Kimhy et al., 2005). A factor analysis of the PDI-21 was followed by cluster analysis of the patient sample, and subsequent comparison of patient subtypes across multiple clinical features: positive symptoms, negative symptoms, substance use, cognition, antipsychotic use, and stress (Adhikari et al., 2019; Burger et al., 1997; Kirkpatrick et al., 2011; Pruessner et al., 2017).

2. Methods

2.1. Study participants

This study involved 286 patients (193 male and 93 female) with SSD: 249 with schizophrenia, 33 schizoaffective disorder, 2 schizophreniform disorder, and 2 unspecified SSD, recruited from clinics at or around the Maryland Psychiatric Research Center. Mean age was 37.4 ± 13.5 years. Diagnoses were made using Structured Clinical Interviews for DSM-IV or 5. Antipsychotic regimens were collected in all patients, except 12 for whom medications could not be ascertained, and 47 for whom specific dosages could not be confirmed. Exclusionary criteria included present/past major medical/neurological conditions and active substance use other than cannabis or tobacco. Recruitment and data collection were in the context of brain imaging protocols, and certain criteria, including current alcohol use, were exclusionary for reasons related to imaging and not necessarily PDI assessment. All participants were evaluated for capacity to provide informed consent and gave written informed consent as approved by the Institutional Review Board of the University of Maryland, Baltimore.

2.2. Clinical symptom assessments

Each item of the PDI-21 consists of a yes/no question. If "yes" is selected, the participant is prompted to complete 3 Likert scales assessing the extent to which this belief is distressing (distress), believed firmly (conviction), and thought about often (preoccupation). The PDI-21 can be scored as the total number of "yes" answers (yes/no score, or PDI Y/N), or as the grand total score which summates the distress, preoccupation, and conviction subscores (Peters et al., 2004). The grand total PDI scores for each item were used in this factor analysis, given the intent to measure delusion severity rather than delusion presence/absence. The grand total score has shown discriminative power over the yes/no score for patients with psychosis (Sisti et al., 2012).

Patients were assessed using the clinician-rated, 20-item BPRS. Subscores on Thought Disturbance, Withdrawal, Anxious-Depression, Hostility-Suspiciousness, and Activation were calculated (Burger et al., 1997). For a Positive Symptom measure, BPRS items 4, 7–8, 11–12, 15, and 20 were summated. Negative symptoms were assessed by using the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011). BPRS and BNSS raters were trained for reliability to gold-standard as previously described (Chiappelli et al., 2014).

2.3. Cognition assessment

Participants completed the Digit Symbol Coding task of the Wechsler Adult Intelligence Scale, third edition (Wechsler, 1997), and the Digit Sequencing test (Keefe et al., 2004). These tasks correspond to processing speed and working memory, respectively—two of the cognitive domains most affected in schizophrenia (Kochunov et al., 2017).

2.4. Substance use assessment

Tobacco smoking status was classified as nonsmoker, ever smoker (>100 cigarettes, lifetime), past smoker, or current smoker. Cigarettes per day (CPD) was used to assess smoking severity. Patients were assessed on current and past cannabis use via structured clinical interviews for the DSM-IV or 5. Lifetime diagnoses of cannabis use or dependence by DSM-IV were considered as Cannabis Use Disorder in accordance with DSM-5 terminology (APA, 2013).

2.5. Past major life stressors

To assess experience of stressful life events, we adapted items from the Life Stressors Checklist-Revised (Wolfe et al., 1996). Participants identified whether they had experienced a given stressor and estimated their age at the time of the stressor. The total number of different types of events, ranging from 0 to 10, was reported as the participant's stressful major life events (MLE) score.

2.6. Statistics

Explorative factor analysis (EFA) with oblimin rotation was

performed on the PDI-21 using the *psych* package in R-3.6.2 (Revelle, 2015). The Kaiser-Meyer-Olkin test assessed sampling adequacy and the Bartlett test of sphericity assessed suitability. We used the scree test, Horn's parallel analysis, and Velicer's minimum average partial approach (MAP) (Horn, 1965; Velicer, 1976) to determine the number of factors. Item factor loadings were thresholded at 0.4. Delusion factor scores were then calculated for each participant as the sum of all loaded items. As factors differed in number of loaded items, normalized Factor Severity Scores were calculated by dividing the factor score by the highest possible score on a given factor.

We then performed k-means clustering to classify patients into delusion subtypes with the above generated factor scores as classification variables. To determine optimal k-value, we used the elbow method (Vergara et al., 2020) to determine the point of diminishing reduction in the Total Within Cluster Sum of Square (WCSS) as cluster numbers increased from k = 1 to k = 10 (Fig. S1). Cluster analyses were set to iterate until convergence with maximum iterations = 25.

Linear regression was used to test for association between factor scores and clinical measures, with age and sex as covariates. ANCOVA and chi square tests were used to compare patient subtypes on continuous (e.g., clinical) and categorical (e.g., smoking status) variables respectively, with age and sex as covariates. Whenever a significant association was found in the overall model, Bonferroni-corrected post-hoc tests were used for pairwise comparisons. When the 5 subscales of the BPRS were tested in tandem for association with patient subtypes, Bonferroni correction for the 5 comparisons was used to adjust p-values. Statistical analyses were performed in SPSS v27.

3. Results

3.1. Exploratory analysis of the PDI-21 structure

The sample was found to be suitable for EFA based on the Kaiser-Meyer-Olkin measure of sampling adequacy (0.90) and Bartlett test of sphericity ($p < 0.001$). By the scree test (Fig. S1A), EFA identified 4 factors with Cronbach's alphas ranging from good (0.85, factor 1) to acceptable (0.65, factor 4) (Hair et al., 2006). Horn's Parallel Analysis also indicated the appropriateness to retain four factors (Fig. S1B). Velicer's MAP suggested only a 2-factor solution, which may indicate that the first 2 factors of the 4-factor solution were stronger, while the 3rd and 4th factors were relatively weak. Items loaded to each factor shared features (Table 1). Factor 1 contains items associated with paranoia or persecution. Factor 2 items are associated with grandiosity or hyperreligiosity. Factor 3 items involve a disrupted experience of self. Factor 4 items center around low self-worth. Accordingly, we named these 4 factors Paranoia, Grandiosity, Selfhood Disruption, and Low Self-Worth.

3.2. Clustering into patient subtypes by delusions

K-means clustering then allowed for sub-grouping of the SSD patient sample according to their delusion factors. A k = 4 was selected as the midpoint of inflection according to the elbow plot (Fig. S1C). The K-means yielded four clusters (centers plotted in Fig. S2). These clusters were identified as: (1) a subtype with low scores across all four delusion factors, named Low-Delusion, (2) a subtype with Grandiose-Predominant delusions, (3) a subtype with Paranoid-Predominant delusions, and (4) a subtype with high scores across delusion factors, named Pan-Delusion (Fig. 1).

3.3. Assessment of basic clinical features across delusion subtypes

There were no significant differences in age ($F(df = 3, 282) = 1.81$, $p = 0.14$), sex ($\chi^2 = 2.61$, $p = 0.46$), mean chlorpromazine (CPZ) equivalents ($F(df = 3, 221) = 0.21$, $p = 0.89$), or whether patients were prescribed clozapine ($\chi^2 = 1.52$, $p = 0.68$) (Table S1).

Table 1
Exploratory Factor Analysis of the PDI in SSD. Items from the PDI-21 are summarized by key theme (Item). A 4-factor solution is proposed. Loading scores with absolute value > 0.1 are shown; loading scores are bolded when meeting threshold of >0.4 and considered loaded to the corresponding factor. Items loaded to each factor show shared features which are named at the bottom of the table.

Item	Factor 1	Factor 2	Factor 3	Factor 4
1. hints/double meaning	**0.807**	−0.111		
2. special messages from TV	**0.434**	0.136	0.303	0.147
3. people not what they seem	**0.511**	0.113		0.316
4. persecuted	**0.800**		−0.133	
5. conspiracy	**0.780**			
6. being someone very important		**0.664**		0.155
7. special or unusual person	0.284	**0.603**		0.132
8. especially close to God	−0.125	**0.867**		
9. telepathic communication	**0.473**	0.15	0.338	−0.322
10. influenced by electrical devices		0.246	**0.501**	
11. chosen by God		**0.843**		−0.135
12. belief in witchcraft/voodoo	0.245	0.309	0.201	−0.151
13. partner unfaithful				**0.723**
14. sinned more than average		0.11	0.239	**0.495**
15. people looking oddly at you	0.400		0.154	**0.455**
16. no thoughts in head	−0.212		**0.599**	0.255
17. world about to end	0.28	0.281	0.156	0.133
18. thoughts feel alien	0.139		**0.705**	
19. thoughts overheard	0.345		0.399	
20. thoughts echoing back			**0.672**	
21. being a robot/ zombie			**0.631**	0.173
Common Features	Paranoia	Grandiosity	Selfhood Disruption	Low Self Worth

Significant subtype differences were found on clinician-assessed symptoms. On the BPRS, the Anxious-Depression subscore showed significant effect of subtype ($F(3, 267) = 12.07$, $p = 9.8 \times 10^{-7}$), with Pan-Delusion showing the highest symptoms, followed by Paranoid-Predominant (Fig. 2A). The Hostile/Suspiciousness subscore similarly showed significant subtype effect ($F(3, 268) = 11.66$, $p = 1.7 \times 10^{-6}$, Fig. 2D), with Pan-Delusion and Paranoid-Predominant subtypes scoring highest. The Thought Disturbance subscale, on which clinicians assesses thought disorder and unusual thought content, showed significant effect of subtype ($F(3, 263) = 11.02$, $p = 3.8 \times 10^{-5}$), with the Low-Delusion subtype scoring lower than the other 3 (all $p < 0.05$) (Fig. 2C). Subtypes did not differ significantly on the BPRS subscales of Withdrawal nor Activation (Fig. 2B and **E**). Concerning negative symptoms as assessed via the BNSS (Fig. 2F), the model was significant ($F(3, 259) = 2.97$, $p = 0.033$), with total scores significantly higher in Low-Delusion compared to Paranoid-Predominant patients ($p = 0.045$). Overall, delusion-based clustering revealed patient subtypes with clinically identifiable differences in schizophrenia symptoms.

3.4. Delusion subtype and cognition

There was significant effect of subtype on processing speed ($F(3, 253) = 3.67$, $p = 0.013$) (Fig. 3A). Post-hoc testing showed higher processing speed in Paranoid-Predominant compared to Low-Delusion subtype ($p = 0.012$). We further explored the relationships between

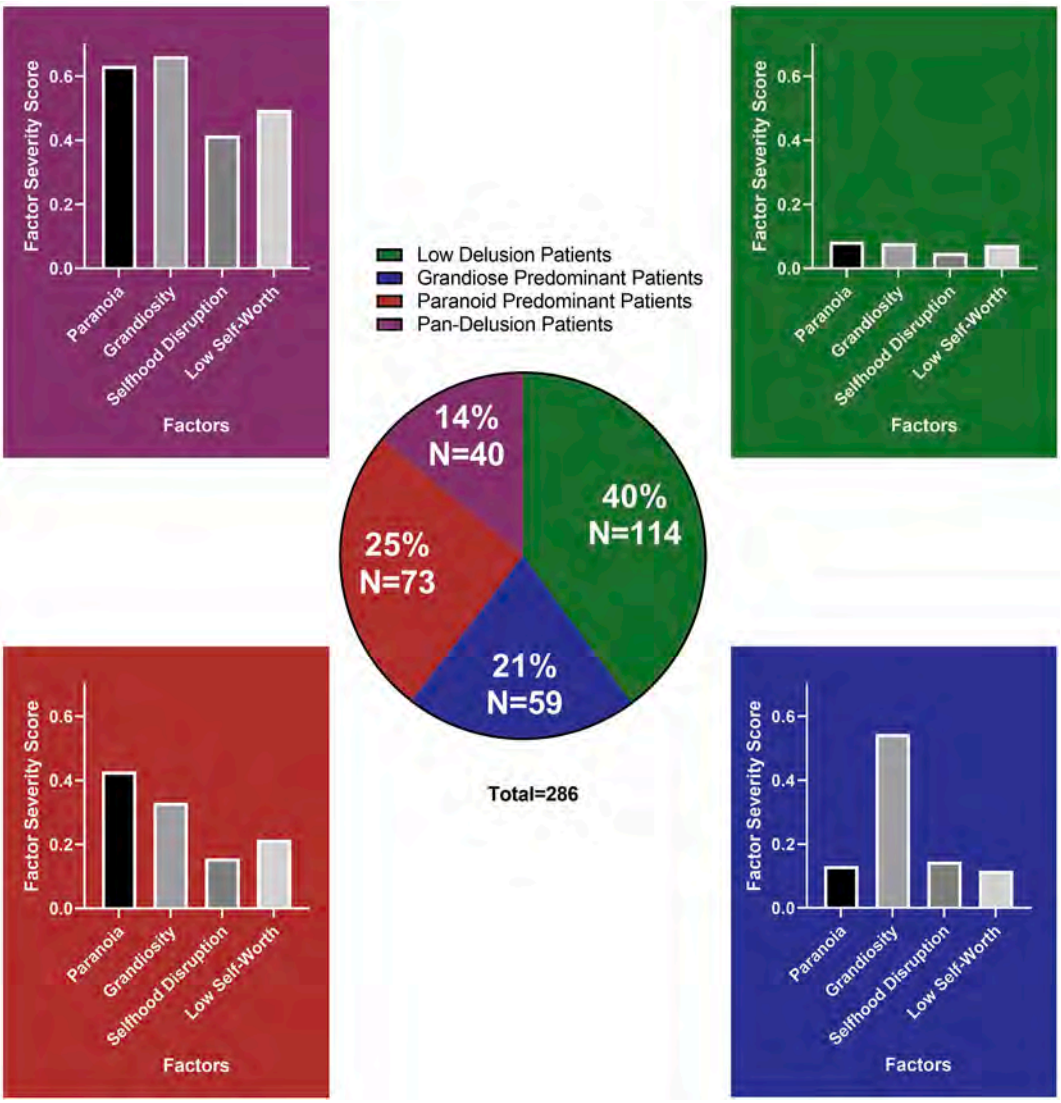

Fig. 1. Delusion-Based Clusters of Patients with SSD. PDI-21 items were reduced to 4 delusion factors, such that all patients were scored on the factors of Paranoia, Grandiosity, Selfhood Disruption, and Low Self-Worth. Factor Severity Scores are calculated as the patient's sum score on the PDI items within a delusion factor, divided by the maximum possible score on these items. Clustering analysis was then used to subtype patients according to their delusion factor scores. This resulted in 4 Clusters of patients which are color coded in the figure. The pie chart in figure middle shows the distribution of total ($N = 286$) patients into the 4 Clusters. Corresponding bar graphs show the mean Factor Severity Scores of patients in each cluster. The Pan-Delusion Cluster (upper left; purple) is defined by the highest relative scores across all delusion factors, whereas the Low Delusion Cluster (upper right; green) is defined by relatively low scores across all delusion factors. The Paranoid Predominant and Grandiose Predominant Clusters (red and blue respectively) are defined by their relative peak delusion factor severity score.

processing speed and the factor scores in the full sample. Only the Paranoia factor was found to have a significant association with processing speed ($r = 0.15$, $p = 0.016$) (Fig. 3B), further suggesting that paranoia as a trait is associated with higher processing speed across SSD patients.

For working memory, there was also a significant subtype effect ($F(3, 255) = 4.32$, $p = 0.005$) (Fig. 3C). Post-hoc testing showed Paranoid-Predominant patients performing significantly better than Grandiose-Predominant ($p = 0.002$) and Low-Delusion ($p = 0.033$) patients. We further explored the relationships between working memory and the factor scores. Only the Paranoia factor showed significant association with working memory ($r = 0.12$, $p = 0.046$) (Fig. 3D).

3.5. Delusion subtypes and cigarette and cannabis use

Current smoking (χ^2 (3) = 2.02, $p = 0.569$) and historical smoking (χ^2 (3) = 3.63, $p = 0.304$) did not significantly differ according to subtype. Among current nicotine smokers ($N = 112$), subtype was significantly associated with smoking severity ($F(df1,df2) = 3.78$, $p = 0.013$) (Fig. 3E). Grandiose-Predominant patients had significantly higher CPD than Pan-Delusion ($p = 0.018$) and trended higher than Paranoid-Predominant ($p = 0.059$) and Low-Delusion patients ($p = 0.077$).

Lifetime prevalence of Cannabis Use Disorder (CUD) showed significant association with delusion subtype (χ^2 (3) = 11.15, $p = 0.011$) (Fig. 3F). Lifetime CUD diagnosis was present in 42% of Paranoid-Predominant patients, significantly above the proportion of CUD diagnosis among Low-Delusion (19%, χ^2 (1) = 10.56, $p = 0.0012$), and suggestively above CUD prevalence among Grandiose-Predominant (25%, χ^2 (1) = 3.82, $p = 0.051$), and Pan-Delusion (24%, χ^2 (1) = 2.96, $p = 0.086$) patients. When Paranoid-Predominant patients were compared to pooled patients of the other 3 subtypes, 2 × 2 chi-square showed significant difference (CUD in pooled patients = 22%, χ^2 (1) = 10.56, $p = 0.0012$), indicating increased prevalence of lifetime CUD in Paranoid-Predominant patients.

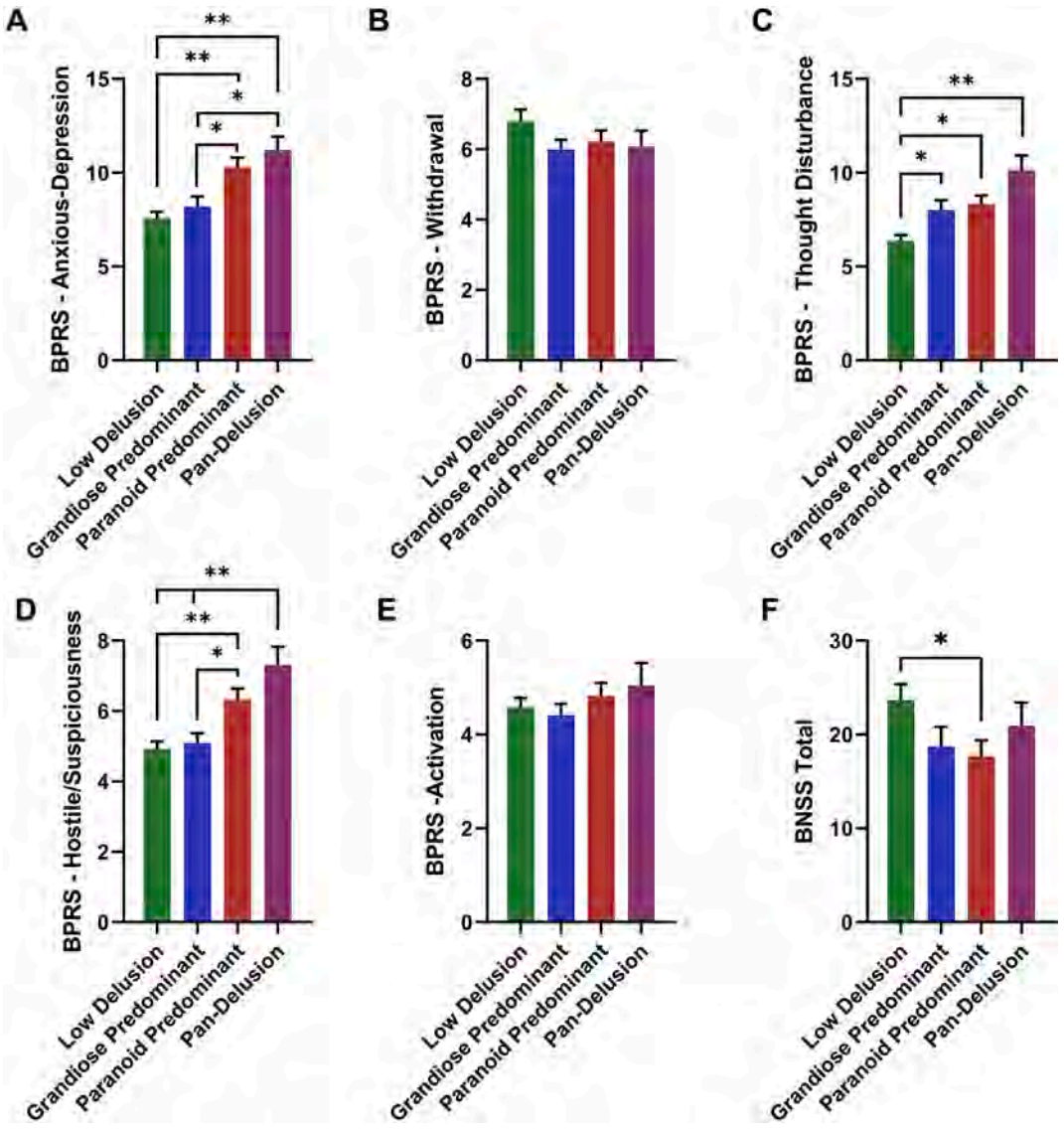

Fig. 2. Clinician Rated Symptoms Align with Cluster-defined Patient Subtypes. Brief Psychiatric Rating Scale (BPRS) subscores that showed significant effect of delusion subtype were (A) anxious-depression, (C) thought disturbance and (D) hostile-suspiciousness. Brief Negative Symptom Scale (BNSS) score showed significant effect of subtype on negative symptoms. Results of Bonferroni corrected post-hoc comparisons between groups are indicated on the graphs (*corrected $p < 0.05$; **corrected $p < 0.001$).

3.6. Stressful major life events

MLE showed significant association with subtype (F (df1,df2) = 8.97, $p = 1.1 \times 10^{-5}$) (Fig. 3G). Pan-Delusion patients showed significantly higher MLE than Low Delusion ($p = 5.7 \times 10^{-5}$) and Grandiose-Predominant patients ($p = 0.036$). Paranoid-Predominant patients had higher MLE than Low-Delusion patients ($p = 1.1 \times 10^{-3}$).

4. Discussion

We subtyped 286 SSD patients using delusion self-report and combined factor and cluster analyses. To our knowledge, this is the largest study of the PDI-21 factor structure in schizophrenia, and the only to clinically characterize resultant subtypes. Delusions as per the PDI-21 reduced to 4 factors: Paranioa, Grandiosity, Selfhood Disruption, and Low Self-Worth (Table 1). Using these four factors, SSD patients clustered into Low-Delusion, Paranoid-Predominant, Grandiose-Predominant, and Pan-Delusion subtypes. Subtypes were differentiated on clinical symptom severity, cognitive performance, stressful life events, and nicotine and cannabis use profiles, as summarized in Fig. 4.

The characterization of clinical features by factor analysis followed by cluster analysis has been used for other neuropsychiatric conditions, e.g. movement disorders (Martinez-Martin et al., 2020), intellectual disability (Lundqvist et al., 2020), and for schizophrenia symptoms other than delusions (Chen et al., 2020). Regarding delusions, previous factor analyses of PDI have tended toward one-factor solutions in non-clinical populations (Fonseca-Pedrero et al., 2012; Jones and Fernyhough, 2007; Prochwicz and Gaweda, 2015; Wang et al., 2017), but a one-factor solution for PDI-Total could not be confirmed in the previously largest clinical sample (N = 196 schizophrenia patients) (Wang et al., 2017). Importantly, while the PDI was originally designed for capturing non-clinical delusion ideation, it robustly distinguishes patients with clinical psychosis (Peters et al., 2004; Sisti et al., 2012), and has since been used to quantify schizophrenia risk and clinical delusion severity (Preti et al., 2007; Tuominen et al., 2022). Thus understanding the internal structure of the PDI as applied to schizophrenia patients is an important validation step.

Cronbach's alphas of the 4-factor solution were good to modest, with the lowest value (Factor 4) = 0.65, although the factors showed internal cohesion that is well-matched with clinical experience. The first two

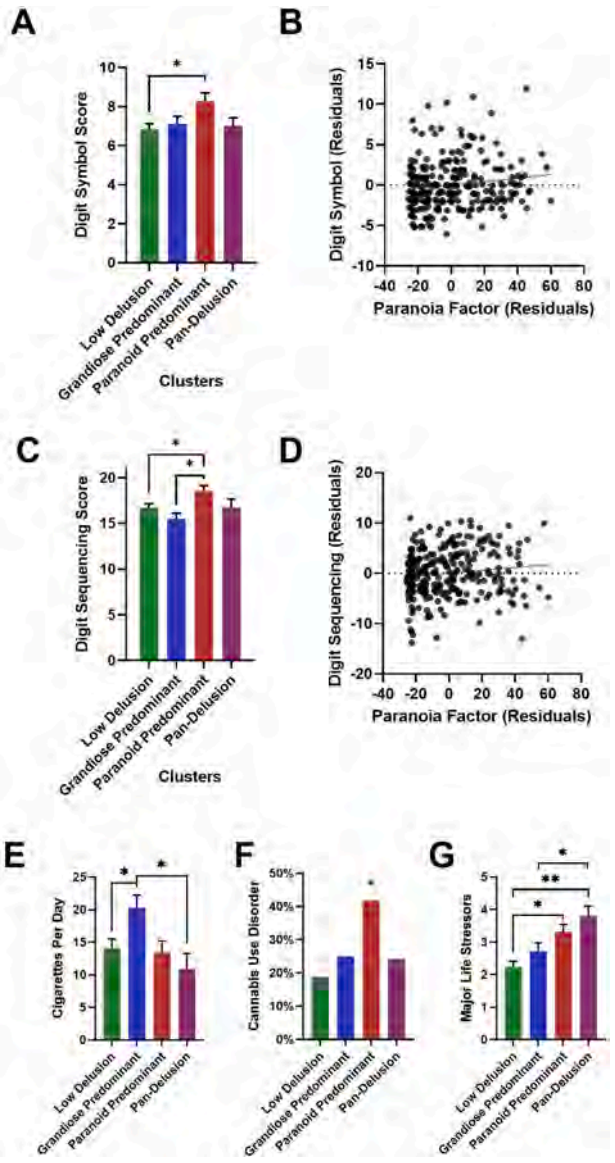

Fig. 3. Relationship between delusion subtypes and cognitive measures, substance use, and life stressors. A. Significant effect of delusion subtype on processing speed as assessed by Digit Symbol Coding task. Paranoid Predominant patients performed significantly better than Low Delusion patients (*corrected $p < 0.05$). B. Among all SSD patients, paranoia factor score showed significant positive association with Digit Symbol score ($p = 0.016$) in linear regression. C. Significant effect of delusion subtype on working memory as assessed by the Digit Span Sequencing task. Paranoid predominant patients performed significantly better than higher scores than Low Delusion and Grandiose Predominant patients (*corrected $p < 0.05$). D. Among all SSD patients, paranoia factor score showed significant positive association with Digit Sequencing score ($p = 0.046$) in linear regression. E-G. Nicotine Use, Cannabis Use History, and Major Life Stressors. E. Among current tobacco smokers, there was significant effect of delusion subtype on Cigarettes Per Day (CPD). Grandiose Predominant patients had significantly higher CPD than Pan-Delusion patients (*corrected $p = 0.018$) with trend of higher CPD than Paranoid Predominant (corrected $p = 0.059$) and Low Delusion patients (corrected $p = 0.077$). **F.** Lifetime diagnosis of Cannabis Use Disorder was present in 42% of Paranoid Predominant, significantly above the pooled prevalence (22%) of the 3 other patient subtypes ($\chi^2 = 10.56$, $p = 0.0012$). **G.** Past major stressors are significantly associated with delusion subtype, where pairwise comparisons show significantly more past stressors in Pan-Delusion patients than Low Delusion (**corrected $p = 0.000057$) and Grandiose Predominant patients (*corrected $p = 0.036$). Paranoid Predominant patients had more past stressors than Low Delusion patients (**corrected $p = 0.0011$).

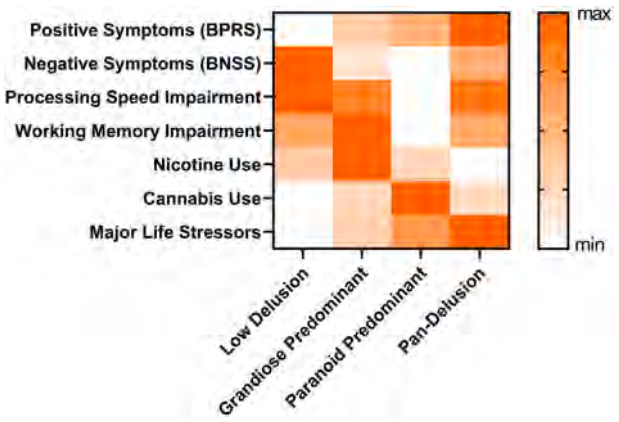

Fig. 4. Comparison of Delusion-Based Patient Subtypes Across Symptomatic and Behavioral Measures. Heat-weighting was normalized to maximum mean value (orange) and minimum mean value (white) within each measure (row).

factors are consistent with Paranoid and Grandiose delusions frequently encountered in clinical practice. The third factor, Selfhood Disruption, is reminiscent of Schneiderian "first-rank" delusions (Silverstein and Harrow, 1981) as it involves a fundamental disturbance in the individual's experience of self, or "ipseity" (Sass and Parnas, 2003). The fourth factor contains items concerned with jealousy, guilt, and the notion that "people look at you oddly because of your appearance." This factor was called Low Self-Worth given the common feature of negative self-evaluation.

With the factor analysis supporting a valid internal structure of the PDI in patients, an important goal was reducing the clinical heterogeneity of SSD via delusion-based subtyping. The 4 patient subtypes we identified via cluster analysis (Low-Delusion, Grandiose-Predominant, Paranoid-Predominant, Pan-Delusion) are remarkably similar to those found in a prior latent class analysis of the PDI in 82 patients with a psychotic disorder and 210 matched controls (Rocchi et al., 2008). That study identified 4 classes: a "normative group" with minimally endorsed items, a "paranoid" class, a "grandiose" class, and a class with high probability of endorsing nearly all items. The current study thus replicates all 3 non-normative (delusion-positive) classes, and suggests that within the SSD population, a patient subgroup with minimally endorsed delusions may represent a negative-symptom-predominant, i.e. deficit-state schizophrenia.

We explored how these subtypes relate to broader clinical features (Fig. 2, Table S1). The Paranoid-Predominant and Pan-Delusion subtypes showed greater severity of anxious-depression and hostile-suspiciousness symptoms. The Low-Delusion group showed low burden of thought disturbance but the highest burden of negative symptoms (Fig. 2C–F). Thus patient clusters identified from delusion self-report showed coherent differences on symptoms as assessed by clinicians. This suggests validity to the clusters, and to delusion self-report.

Beyond clinician-assessed symptoms, these delusion-based subtypes map to distinct clinical features in domains other than delusions. Paranoid-Predominant and Pan-Delusion patients experienced significantly more lifetime stressors compared to the other subtypes (Fig. 3G), coinciding with their higher anxious-depression and hostility symptoms (Fig. 2A–D). Paranoid-Predominant patients showed relatively better processing speed and working memory performance (Fig. 3A–C), suggesting this subtype shows relatively intact cognition. Another feature of this subtype is the increased prevalence of Cannabis Use Disorder (Fig. 3F). There is ongoing debate on the potential causal relationship between cannabis use and schizophrenia (Johnson et al., 2021). Although the cross-sectional nature of the study cannot differentiate causality, cannabis intoxication is known to cause acute paranoia

(Freeman et al., 2015), so the overrepresentation of Cannabis Use Disorder specifically in Paranoid-Predominant patients is intriguing. A hypothesis generated herein might be that disordered cannabis use increases the likelihood specifically of paranoid-type delusion crystallization, but this needs to be tested.

In contrast, the Grandiose-Predominant patient subtype showed increased nicotine use severity (Fig. 3E). Comorbid tobacco use disorder is well-known in schizophrenia, but it is not commonly known whether patients with grandiose delusions are more vulnerable (Fornaro et al., 2022). Speculatively, grandiose delusions may correspond to a subjective feeling of invincibility, manifesting as impulsive or risk-taking behaviors such as smoking; this too would require additional research.

Finally, the Low-Delusion subtype showed several interesting features. Their lower reporting of major life stressors (MLE) could be interpreted according to the stress-diathesis mechanism wherein major life stressors are both a cause and an effect of more severe delusion symptoms (Donaldson et al., 2022). The Low-Delusion subtype showed significantly lower scores on multiple symptom measures and overall positive symptoms of psychosis (Fig. 2A, C-D, Fig. 4), but the highest mean score on negative symptoms (Fig. 2F). Therefore, the lower MLE could alternatively be interpreted as a result of more social withdrawal due to negative symptoms, decreasing the likelihood of interpersonal stressors. The Low-Delusion group also showed relative impairment on cognitive tasks (Fig. 3A–C), further suggesting features of deficit-type schizophrenia (Ahmed et al., 2015) in this subtype.

This study has several limitations and caveats. The use of single timepoint measures makes it difficult to assess the causality of these subtypes in relationship to clinical features. While prior studies of the PDI-21 have found temporal stability (Wang et al., 2017), longitudinal measures would be invaluable for determining the extent of prognostic implications. The use of delusion content to subtype patients could be problematic because belief content varies across cultures and time periods. However, it may be that the underlying subjective states are more universal, despite specific delusional beliefs varying by culture. Paranoia, for example, has been shown to be the most prevalent delusion type irrespective of culture or time period (Skodlar et al., 2008; Stompe et al., 1999). Another limitation is in interpreting the differential severity of tobacco use and prevalence of cannabis use disorder among delusion subtypes; these analyses were conducted without an a priori hypotheses, but rather for hypothesis-generating purposes. Antipsychotic medication was not prospectively controlled in these patients across subtypes, leaving open the question whether some of the subtypes were the consequences of differential treatments. For example, Low-Delusion patients may originally have low level of delusions or be responders to the antipsychotics they are taking, while Pan-Delusion patients might represent treatment-refractory cases. Prospective studies are needed to resolve these questions. However, we found no statistical difference in current CPZ dose or proportion of clozapine use across these subtypes (Table S1). Finally, the PDI grand total score used here is a composite score of distress, preoccupation, and conviction, and it has been suggested that separate cognitive and emotional processes underlie each of these features (Garety et al., 2005). Given that specific latent variables may differ between these domains, separate factor analyses of PDI distress, preoccupation, and conviction scores, as compared to the factors identified from the grand total, would be justified for psychometric purposes. For the purposes of the current study, a presupposition was the existence of a shared latency, e.g. the salience associated with a given type of delusion, that might manifest as preoccupation, conviction, distress, or any combination thereof, and thereby determine clinical severity.

Diagnostic subtypes of schizophrenia, including "Paranoid Schizophrenia," were removed in DSM-5 (Mattila et al., 2015). Rationale included the lack of consistency and stability in subtype diagnoses over time, lack of difference in cognitive or other characteristics, and lack of predictive value of subtype diagnoses for treatment and prognosis (Mattila et al., 2015). However, these issues may have stemmed from a lack of diagnostic reliability due to non-standardized subtyping approaches (Aboraya et al., 2018). Meanwhile there is continued recognition that schizophrenia is highly heterogenous, and parsing heterogeneity is key to advancing etiology and treatment research (Fischer and Carpenter, 2009; Gratton and Mittal, 2020).

Evidence from this study suggests utility in maintaining attention to delusion typology. It also suggests that at least in a cross-sectional sample, the Paranoid-Predominant form of SSD may indeed be a distinct entity, with relatively intact cognition being a notable characteristic. Other novel hypotheses generated include that patients with monothematic grandiose delusions may benefit from increased screening/interventions related to tobacco use, and that cannabis use may be a risk factor for monothematic paranoid delusions in prone individuals. It may also be prudent to conduct risk assessments for hostility among those that present with paranoid or pan-delusions. Further, subtypes may have implications for psychosocial treatments. For example, persecutory delusions are maintained by excessive worry, anxious avoidance, sleep dysfunction, negative self-beliefs, and reasoning bias (Freeman, 2016; Freeman et al., 2016). Psychological treatments targeting these features has reduced delusion conviction and severity (Freeman et al., 2021), and may therefore be indicated for Paranoid-Predominant subtype. For the Low-Delusion subtype, recent investigations have found cognitive-behavioral therapy (CBT) to have limited impact on negative symptoms (Velthorst et al., 2015), and so interventions such as social skills training, compensatory cognitive training, and behavioral activation may prove more beneficial (Granholm et al., 2022).

Whether and to what degree the delusion-based subtypes outlined here correspond to separate pathways on the level of neural circuitry will need to be addressed for biological grounding. The results in this study encourage formal delusion subtyping efforts that may refine clinical profiles towards reducing the heterogeneity of SSD for clinical practice and research.

Funding sources and conflicts of interest

LEH has received or plans to receive research funding or consulting fees on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho, Heptares, Pfizer, Luye Pharma, IGC Pharma, Sound Pharma, Regeneron, and Takeda. All other authors declare no conflict of interest. Support was received from the National Institutes of Health (grant R01MH116948, UH3DA047685, P50MH103222 and the University of Maryland/Sheppard Pratt Psychiatry Residency PSTP Program).

CRediT authorship contribution statement

Andrew D. van der Vaart: Conceptualization, Formal analysis, Visualization, Writing- Original draft preparation. **Yizhou Ma:** Software, Formal analysis, Validation, Writing – review & editing. **Joshua Chiappelli:** Investigation, Data curation. **Heather Bruce:** Investigation, Data curation. **Mark D. Kvarta:** Data curation, Supervision, Writing – review & editing. **Alia Warner:** Writing – review & editing. **Xiaoming Du:** Supervision. **Bhim M. Adhikari:** Supervision. **Hemalatha Sampath:** Project administration, Data curation. **Peter Kochunov:** Investigation, Resources, Writing – review & editing. **L. Elliot Hong:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LEH has received or plans to receive research funding or consulting fees on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho, Heptares, Pfizer, Luye Pharma, IGC Pharma, Sound

Pharma, Regeneron, and Takeda. All other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.12.025.

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