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Transformed PANSS Factors Intended to Reduce Pseudospecificity Among Symptom Domains and Enhance Understanding of Symptom Change in Antipsychotic-Treated Patients With Schizophrenia

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Positive and Negative Syndrome Scale (PANSS) total score is the standard primary efficacy measure in acute treatment studies of schizophrenia. However, PANSS factors that have been derived from factor analytic approaches over the past several decades have uncertain clinical and regulatory status as they are, to varying degrees, intercorrelated. As a consequence of cross-factor correlations, the apparent improvement in key clinical domains (eg, negative symptoms, disorganized thinking/behavior) may largely be attributable to improvement in a related clinical domain, such as positive symptoms, a problem often referred to as pseudospecificity. Here, we analyzed correlations among PANSS items, at baseline and change post-baseline, in a pooled sample of 5 placebo-controlled clinical trials (*N* = 1710 patients), using clustering and factor analysis to identify an uncorrelated PANSS score matrix (UPSM) that minimized the degree of correlation between each resulting transformed PANSS factor. The transformed PANSS factors corresponded well with discrete symptom domains described by prior factor analyses, but between-factor change-scores correlations were markedly lower. We then used the UPSM to transform PANSS in data from 4657 unique schizophrenia patients included in 12 additional lurasidone clinical trials. The results confirmed that transformed PANSS factors retained a high degree of specificity, thus validating that low between-factor correlations are a reliable property of the USPM when transforming PANSS data from a variety of clinical trial data sets. These results provide a more robust understanding of the structure of symptom change in schizophrenia and suggest a means to evaluate the specificity of antipsychotic treatment effects.

Key words: schizophrenia/antipsychotic agents/factor analysis/efficacy/clinical

Introduction

Schizophrenia is a chronic and disabling disorder with a heterogeneous clinical presentation characterized by symptoms across a range of psychological, behavioral, and cognitive domains. A DSM-5 diagnosis of schizophrenia may include the presence of positive symptoms (delusions or hallucinations), negative symptoms (diminished emotional expression or avolition), or disorganized thinking/behavior (disorganized speech or grossly disorganized behavior or catatonia). Symptoms associated with the diagnosis often occur within 2 additional domains of depression/anxiety and hostility/excitement.

Since its introduction in 1987,[1] the Positive and Negative Syndrome Scale (PANSS), consisting of 30 items, has been the most widely used measure of illness severity, and the PANSS total score is the gold standard primary efficacy measure in acute treatment studies of schizophrenia. Factor analyses of the PANSS[2–6] have consistently identified 5 factors which map on to DSM-5 core criteria of positive symptoms, negative symptoms, disorganized thinking and the associated symptom domains of hostility/excitement, and depression/anxiety.

Both first and second generation antipsychotic medications have demonstrated significant efficacy in the treatment of positive symptoms of schizophrenia[7], hostility/excitement[8,9] and (to a lesser degree) symptoms of depression/anxiety.[7] However, comparably effective treatment of negative symptoms and cognitive dysfunction remains an unmet need.[10,11] A major focus of current research efforts is the development of antipsychotic medications with the potential to improve negative symptoms and cognitive dysfunction. Several candidate agents appear to act by mechanisms not limited to dopamine receptor blockade.[12,13]

A significant impediment to correctly characterizing the efficacy of new drugs for the treatment of specific

symptom domains (eg, negative symptoms or cognitive dysfunction) is the extent to which PANSS factors are correlated with each other.[14] As a consequence, it is difficult to determine whether improvement in the severity of symptoms in the 5 PANSS factors is a domain-specific treatment effect, or is a nonspecific effect secondary to observed improvement in correlated PANSS items.[3,11,15–17] It is also possible, though it seems unlikely, that the high degree of between-factor correlation may indicate that a single neurobiological effect (eg, dopamine dysregulation) might underlie the respective changes measured across the PANSS Marder domains.

In an attempt to address this pseudospecificity problem,[18,19] research efforts have been directed toward the development and validation of domain-specific assessment measures that exhibit minimal to no correlation with other schizophrenia symptom domains. These include measures of negative symptoms such as the Negative Symptom Assessment Scale,[20–24] and measures of cognitive dysfunction such as the MATRICS Consensus Cognitive Battery.[25,26] Research Domain Criteria (RDoC) have also been proposed, in part, in an effort to discover therapies that might be more fundamental to the neurobiology of a disorder such as schizophrenia.[27]

An alternative approach, which leverages decades of existing treatment research, is to retain the PANSS as an efficacy measure while attempting to minimize the degree of correlation between each PANSS factor (which are traditionally comprised of selected PANSS items that are equally weighted). To accomplish this aim, we adjusted the weights of individual PANSS items that contribute to each factor using factor analysis procedures, on a pooled sample of 5 placebo-controlled lurasidone clinical trials, to identify a score matrix of coefficients for each PANSS item. The uncorrelated PANSS score matrix (UPSM) that was derived from these analyses was used to generate transformed PANSS factors. Analyses confirmed that the transformed PANSS factors exhibited minimal between-factor correlation, while retaining a high degree of correspondence with standard PANSS factors. The UPSM used to generate transformed PANSS factors was then independently validated in 12 separate clinical trials in schizophrenia consisting of an additional 4657 unique patients, thus confirming the potential utility of UPSM for minimizing pseudospecificity.

Methods

The analysis sample consisted of PANSS data derived from 5 similarly designed, randomized, double-blind, placebo-controlled, 6-week treatment studies of lurasidone or active comparator for the treatment of patients with an acute exacerbation of schizophrenia. The 5 studies were previously analyzed by Loebel et al[16] for lurasidone treatment effects on the Marder[3] PANSS factors. Patients ($N = 1710$) were included in the analysis sample if they had received at least one dose of study drug (treatment groups included placebo, lurasidone, quetiapine, or olanzapine) and had at least one postbaseline PANSS assessment.

To visualize the relatedness and clustering among PANSS items from the pool of 5 placebo-controlled studies, Pearson's correlations were calculated for each PANSS item, first for baseline scores, and separately for postbaseline change scores. Dendrograms were then constructed to visually display the relationship among PANSS items, with more highly correlated items shown with shorter pairwise branch distances in a dendrogram. Dendrograms were constructed based on the unweighted average distance method in MATLAB R2016a2 and using a distance metric of $1 - r^2$, where r is the Pearson correlation between 2 items.[28]

A *score matrix* was defined as a matrix of coefficients with dimensions 30 × 7 (30 PANSS items × 7 transformed PANSS factors). The *score matrix* coefficients were identified by adapting a factoring procedure (PROC FACTOR of SAS 9.4[29]) with a maximum likelihood method, rotated using varimax algorithm and compensated for communality greater than 1 using Heywood criteria without a limit on the number of factors produced.[30] The factoring procedure was conducted on an input data matrix of dimensions (N PANSS observations) × (30 PANSS items). PANSS data were obtained from the pool of 5 clinical studies reported by Loebel et al.[16] The factoring procedure was conducted on all PANSS on-treatment data consisting of change-from-baseline to each postbaseline time-point (weeks 1–6), a total of 11 970 PANSS observations in all 1710 subjects from all treatment groups (including placebo, lurasidone, quetiapine, olanzapine).The factoring procedure applied a last observation carried forward (LOCF) data imputation method for missing postbaseline PANSS assessments consistent with previous factor-analytic studies of PANSS.[3] Each of the 7 transformed PANSS factors was identified by their items' correspondence to the dendrogram branches and the 5 Marder PANSS factors. Two of the factors (negative symptoms and depression/anxiety) were further subdivided into subfactors (apathy/avolition and deficit of expression; and depression and anxiety, respectively).

The coefficients of anUPSM identified above were fixed and subsequently used to transform additional PANSS change from baseline data into 7 transformed PANSS factor scores by the following matrix multiplication:

$$[\text{PANSS data}]_{(N\times 30)} \times [\text{UPSM}]_{(30\times 7)} = [\text{Transformed PANSS factor data}]_{(N\times 7)}.$$

Supplementary table S1 provides the coefficients of the $[UPSM]_{(30\times 7)}$.

To independently validate the properties of the UPSM transformation, transformed PANSS factors for 12 separate clinical trials in schizophrenia consisting

of an additional 4657 unique patients were calculated to verify that the UPSM indeed could generate transformed PANSS factors which retained a high degree of specificity/orthogonality across a wide variety of different clinical trial data sets, patient populations, and treatment conditions. Included among the 12 additional clinical trials were short-term acute schizophrenia studies, open-label studies, long-term extension studies, and randomized withdrawal studies, which represent a total of over 47 639 PANSS change score observations. For each study in the validation data set, the transformed PANSS factors were evaluated for their total variance (high *R*-squared values between sums of the transformed PANSS factors vs PANSS total score), specificity/orthogonality (low correlation between the individual transformed PANSS factors), and high face validity (high correspondence with the Marder PANSS factors).

Results

Symptom Dimensions of Schizophrenia at Baseline

Schizophrenia symptoms at baseline in the pooled sample (N = 1710) clustered according to the relative correlations among PANSS items (figure 1). Five domains of psychopathology were evident as clusters of items in 5 major branches of a dendrogram. Individual items demonstrated both positive and negative cross-correlations across each of the 5 Marder PANSS factors (figure 1).

Symptom Dimensions of Schizophrenia: Change from Baseline

Schizophrenia symptoms change scores also clustered according to their relative correlations among PANSS item (change from baseline) scores (figure 2). Domains of psychopathology were evident in a similar pattern of clustering as was observed for PANSS items at baseline. In the negative symptom branches, 2 distinct subfactors (apathy/avolition and deficit of expression) were evident in both change from baseline, and at baseline. Hostility symptoms exhibited similar clustering at baseline, and change from baseline.

An analysis of baseline-to-endpoint change in the current pooled data set revealed substantial correlations among the Marder PANSS factors (table 1). Endpoint (Week 6) change in the Marder PANSS positive factor score was highly correlated with endpoint change in the

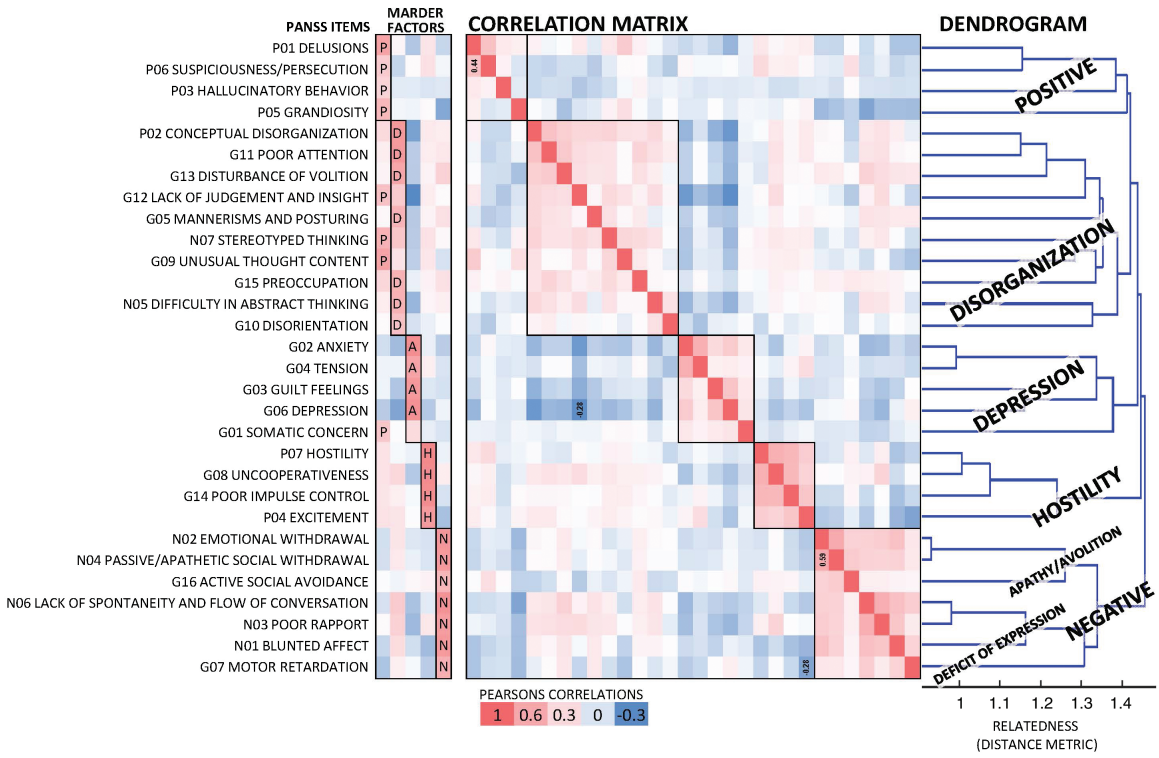

Fig. 1. Correlation matrix heat map of PANSS item scores for all patients at baseline (N = 1710). The dendrogram (far right) displays clustering of related items according to a distance metric, where closely related items were more correlated than distantly related items (x-axis). The branches are labeled according to the clustering of items. Each row corresponds to an item in PANSS (labeled on far left) with identity to each column in the correlation matrix along the diagonal (red). The columns under heading MARDER FACTORS collect correlations between each item rating and each of 5 Marder PANSS factor scores vs rows. Items identified by the Marder model[5] are labeled with letters as follows: P for positive, D for disorganized, A for anxiety/depression, H for hostility, and N for negative. The CORRELATION MATRIX is colored according to Pearson's r value between each item and is symmetrical across the diagonal. Boxed areas identify clusters of items with higher correlations (red) and correspond to the clustering in the dendrogram branches.

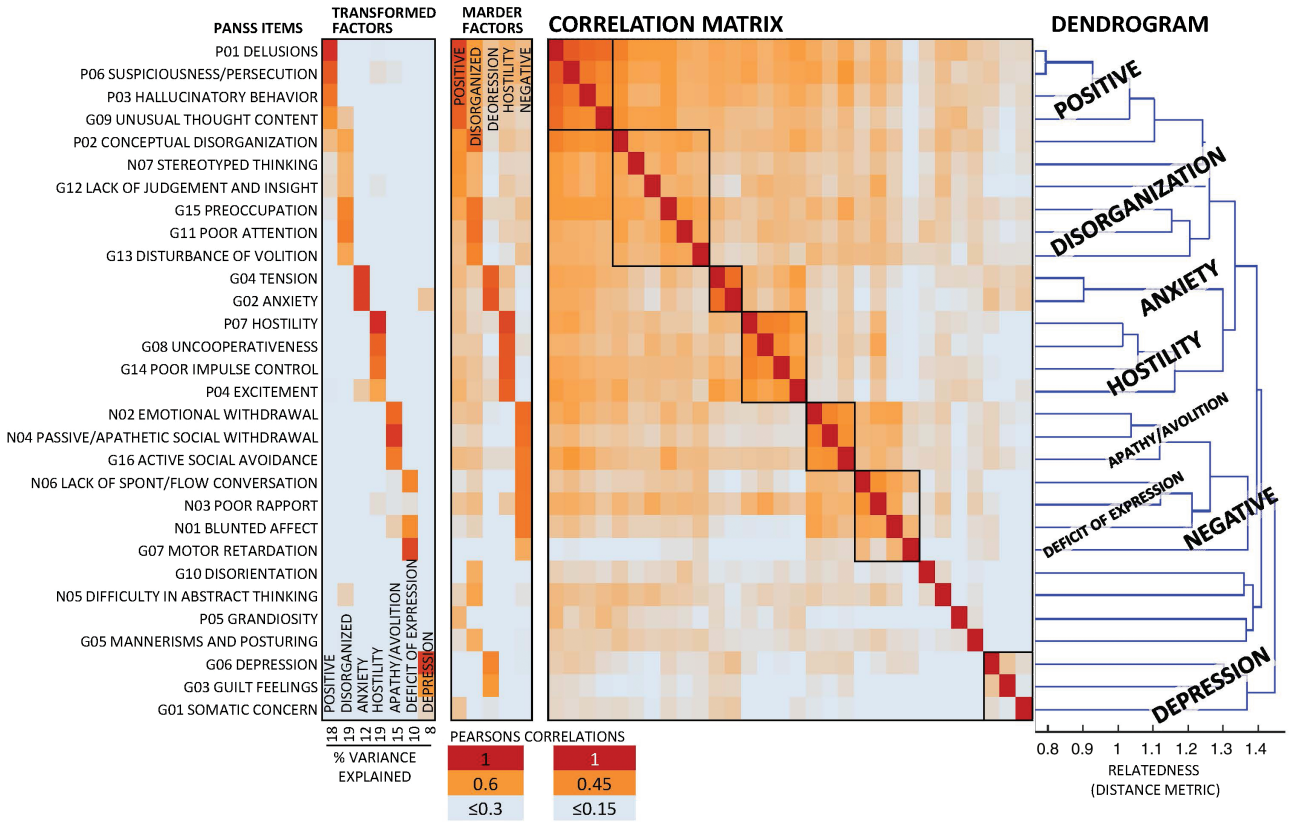

Fig. 2. Correlation matrix heat map of PANSS item scores for all observations' change from baseline. Correlations of individual item change scores (rows) are shown relative to the transformed PANSS factor change scores (columns under heading TRANSFORMED FACTORS), or relative to the Marder PANSS factors. Transformed PANSS factors were calculated using the coefficients of the score matrix (UPSM, supplementary table S1). The relatively low correlations among items outside of their respective (transformed) factor illustrates specific associations of items with distinct transformed PANSS factors, relative to Marder PANSS factor scores which have substantial correlations outside of their respective PANSS factors. The amount of variance explained by each PANSS factor was identified and labeled for each transformed PANSS factor. The CORRELATION MATRIX is colored according to Pearson's *r* value between each item, and corresponds by row to the dendrogram at the far right. Branches in the dendrogram are labeled according to clustering of items, and correspond to boxes along the diagonal of the correlation matrix.

Marder PANSS disorganized thought (r = .74), negative (r = .57), hostile (r = .64), and anxiety/depression (r = .52) factor scores (table 1).

Transforming PANSS Items

Results Using Transformed PANSS Factors. Each of the 7 transformed PANSS factors corresponded preferentially with its related Marder PANSS factor, as illustrated in table 2. The transformed PANSS factor for negative, disorganized, and hostile symptoms were each preferentially correlated with their respective Marder PANSS factors. Two of the Marder PANSS factors (negative symptoms and depression/anxiety) further subdivided in the transformed PANSS factors of apathy/avolition and deficit of expression, and depression and anxiety, respectively.

The amount of variance explained by each transformed PANSS factor is noted in figure 2 with 8% to 19% variance explained by each of the 7 transformed PANSS factor scores. PANSS total scores were well-described by a sum of 7 transformed PANSS factor scores, with estimates from regression analysis yielding R^2 value goodness of fit for $P < .0001$ at .93.

The transformed PANSS factors reduced correlations between the different factors when compared to the correlations observed between the Marder PANSS factors. In table 3, the orthogonality of the transformed PANSS factors is evidenced by the lower correlations between the transformed PANSS factors when compared with the higher off-diagonal correlations of the Marder PANSS factors shown in table 1. Correlations of individual items across Marder PANSS factors were greater (less specific) than the (low) correlations across the transformed PANSS factors (figure 2).

Efficacy Profile Using Transformed Orthogonal PANSS Factors

Placebo effect size estimates (change from baseline to Week 6, within-treatment group) were compared with the Marder PANSS factors (figure 3 top left panel)

Table 1. Correlations Among Marder PANSS Factor Scores (Week 6 Change from Baseline)

Marder PANSS factors	Pos	Dis	Neg	Hos/Exc	Anx/Dep	Tot
Positive Symptoms	1					
Disorganized Thought	0.74	1				
Negative Symptoms	0.57	0.62	1			
Hostility/Excitement	0.64	0.59	0.43	1		
Anxiety/Depression	0.52	0.45	0.40	0.46	1	
PANSS Total	0.90	0.86	0.77	0.77	0.66	1

Note: Pearson's correlation coefficients between all patients' item subtotals for items categorized by factor analysis of Marder et al.[5] PANSS data derived from 5 similarly designed, randomized, double-blind, placebo-controlled, 6-week treatment studies patients with an acute exacerbation of schizophrenia (N = 1710) POS, positive; DIS, disorganized; Neg, negative; Hos/Exc, Hostility/excitement; Anx/Dep, anxiety/depression; Tot, total.

Table 2. Correlations Between Marder Vs Transformed PANSS Factor Scores

	Transformed PANSS factors							
Marder PANSS factors	POS	DIS	NAA	NDE	HOS	ANX	DEP	TOT
Positive Symptoms	**0.79**	0.52	0.24	0.15	0.44	0.28	0.28	0.85
Disorganized Thought	0.44	**0.79**	0.30	0.27	0.39	0.24	0.20	0.79
Negative Symptoms	0.32	0.33	**0.75**	**0.65**	0.28	0.13	0.23	0.78
Hostility/Excitement	0.38	0.30	0.16	0.02	**0.94**	0.29	0.12	0.73
Anxiety/Depression	0.26	0.14	0.17	0.10	0.30	**0.74**	**0.76**	0.73
PANSS Total	0.59	0.55	0.42	0.31	0.57	0.37	0.36	0.97

Note: Pearson's correlation coefficients between the Marder PANSS factor scores vs the transformed PANSS factor scores. PANSS data derived from 5 similarly designed, randomized, double-blind, placebo-controlled, 6-week treatment studies patients with an acute exacerbation of schizophrenia (N = 1710). Transformed PANSS factors were calculated by the uncorrelated PANSS score matrix (UPSM, supplementary table S1). POS, positive; DIS, disorganized; NAA, negative symptoms apathy/avolition; NDE, negative symptoms deficit of expression; HOS, hostility; ANX, anxiety; DEP, depression; Tot, total.

Table 3. Correlations Among the Transformed PANSS Factor Scores (Week 6 Change from Baseline)

Transformed PANSS factors	POS	DIS	NAA	NDE	HOS	ANX	DEP
POSITIVE	1						
DISORGANIZED	0.20	1					
NEG APATHY/AVOLITION	0.10	0.08	1				
NEG DEFICIT OF EXPRESSION	0.04	0.12	0.22	1			
HOSTILITY	0.21	0.12	0.07	-0.02	1		
ANXIETY	0.09	0.04	-0.01	-0.08	0.13	1	
DEPRESSION	0.10	0.00	0.12	0.13	0.04	0.27	1
PANSS TOTAL SCORE	0.60	0.45	0.45	0.36	0.53	0.45	0.46

Note: Pearson's correlation coefficients between the transformed PANSS factor scores. Transformed PANSS factors were calculated by the uncorrelated PANSS score matrix (UPSM, supplementary table S1). PANSS data derived from 5 similarly designed, randomized, double-blind, placebo-controlled, 6-week treatment studies patients with an acute exacerbation of schizophrenia (N = 1710). POS, positive; DIS, disorganized; NAA, negative symptoms apathy/avolition; NDE, negative symptoms deficit of expression; HOS, hostility; ANX, anxiety; DEP, depression; Tot, total.

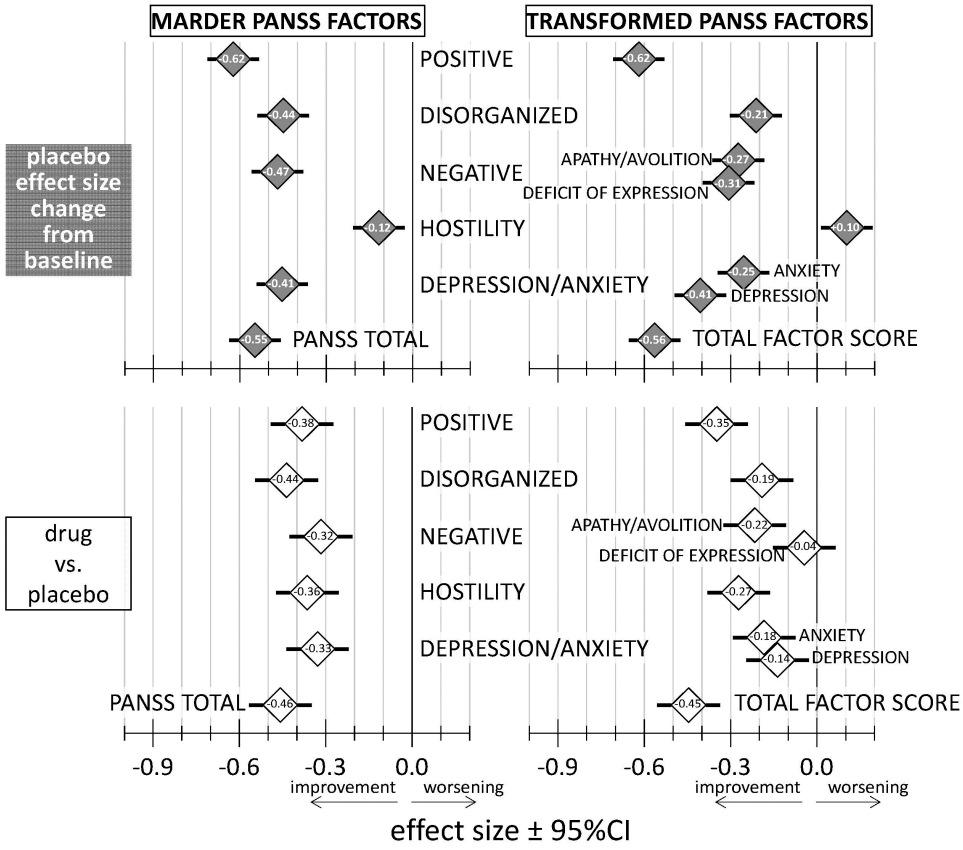

Fig. 3. Top: placebo effect sizes. Profile of improvements (change from baseline) in schizophrenia symptoms estimated using PANSS factors. In the left panel, within-treatment effect sizes (with 95% CI) for placebo are shown for change from baseline at week 6 endpoint, based on the Marder PANSS factors. In the right panel, the same within-treatment effect sizes at endpoint are shown based on the transformed PANSS factors. Transformed PANSS factors were calculated using the coefficients of the score matrix (UPSM, supplementary table S1). Bottom: drug treatment effect sizes. Profile of active drug effects on schizophrenia symptom domains. In the left panel, lurasidone vs placebo effect sizes (with 95% CI) are shown for change from baseline at week 6 endpoint, based on the Marder PANSS factors. In the right panel, the same lurasidone vs placebo effect sizes at endpoint are shown based on the transformed PANSS factors. Drug effects were constructed using a pool of all lurasidone doses (40, 80, 120, or 160 mg/day, total $N = 993$) and excluded active comparators (olanzapine, quetiapine-XR). To examine placebo effects on PANSS factors, placebo treated patients ($N = 484$) were pooled across all studies. Transformed PANSS factors were calculated using the coefficients of the score matrix (UPSM, supplementary table S1).

vs the transformed PANSS factors (top right panel). Placebo effect sizes for positive and depression symptoms were similar between Marder PANSS factor estimates and the transformed PANSS factors. Placebo effect sizes were smaller for negative, disorganized, and anxiety symptoms as estimated with the transformed PANSS factors, and a small worsening was observed for placebo effect on hostility. The placebo effect size for PANSS total score was almost identical as that estimated by the total score of transformed PANSS factors.

Drug treatment effect size estimates (lurasidone vs placebo for baseline-to-endpoint change) were calculated using both the Marder PANSS factors (figure 3; bottom left panel) and the transformed PANSS factors (figure 3, bottom right panel). Marder PANSS factors estimated a relatively consistent pattern of moderate drug effect sizes (ranging from 0.31 to 0.44) across the factors, suggesting similar efficacy across the symptom domains from the viewpoint of the Marder PANSS factors. The transformed PANSS factor estimate for positive symptoms (0.35) was similar to the Marder PANSS factor estimate (0.38), but the drug effect sizes among the transformed PANSS factors exhibited greater contrast between the symptom domains (0.05–0.27) with greater drug effects on positive and hostility symptoms, and smaller drug effects on disorganized, negative apathy/avolition, deficit of expression, and anxiety/depression symptoms.

Cross-study Validation of the Score Matrix Transformation

The UPSM transform, which was identified above, was used to transform PANSS from an additional 4657 unique schizophrenia patients across 12 different clinical trials. Substantially reduced between-factor correlations were observed for each individual study. Table 4 summarizes the properties of the UPSM transform applied to each of the

Table 4. The Uncorrelated PANSS Score Matrix Reduced Correlations Among PANSS Factor Scores in Each of 17 Individual Clinical Studies

Data Set	Study	Design	*N*	Duration	Tot. Factor Score[a] Vs PANSS Total	Transformed PANSS Positive Vs[b]				Marder PANSS Positive Vs[b]		
						DIS	AA	DE	HOS	DIS	NEG	HOS
Original Analysis	D1050006	RCT	132	Week 6	0.91	0.21	−0.03	0.03	0.00	0.72	0.50	0.52
	D1050196		174		0.94	0.25	0.00	−0.02	0.17	0.76	0.51	0.59
	D1050229		471		0.93	0.15	0.09	0.02	0.27	0.71	0.54	0.67
	D1050231		456		0.95	0.20	0.13	−0.02	0.17	0.74	0.56	0.62
	D1050233		477		0.94	0.20	0.16	0.13	0.22	0.75	0.62	0.67
Validation Analysis	D1001002	RCT	455	Week 6	0.95	0.06	−0.04	−0.08	0.24	0.72	0.56	0.74
	D1001056		450		0.96	0.16	0.07	0.08	0.18	0.75	0.65	0.68
	D1050049		325		0.93	0.11	0.09	0.01	0.04	0.69	0.54	0.56
	D1050301		326		0.92	0.00	0.13	−0.02	0.13	0.63	0.55	0.60
	D1050303		402		0.94	0.14	0.09	−0.02	0.17	0.70	0.56	0.59
	D1050307		191	Week 12	0.94	−0.06	0.16	−0.02	0.11	0.61	0.59	0.54
	D1050237		615	Week 28	0.86	−0.08	−0.09	−0.09	−0.07	0.40	0.28	0.28
	D1050290		145	Month 6	0.88	0.06	0.04	−0.30	−0.14	0.48	0.28	0.34
	D1050234		292	Month 12	0.91	0.13	0.16	−0.03	0.17	0.68	0.51	0.62
	D1050238	RWS—DB	284	Week 28	0.94	0.07	0.14	0.05	0.24	0.70	0.61	0.64
	D1050238	RWS—OL	655	Week 24	0.91	0.08	0.16	0.02	0.09	0.65	0.55	0.59
	D1050289	OL	236	Week 6	0.86	−0.01	−0.03	−0.12	−0.02	0.40	0.31	0.32
	D1001057		281	Week 26	0.95	0.10	0.01	−0.08	0.18	0.75	0.61	0.72

Note: The uncorrelated PANSS score matrix (UPSM) identified using a pool of trials in the "Analysis" data set was used to transform PANSS from each individual study, including 12 additional clinical trials listed in the "Validation" data set. RCT, randomized placebo-controlled trial in acute schizophrenia; RWS, randomized withdrawal study at endpoint of open label or double blind period. All studies were adults with schizophrenia except for D1050301 which was adolescents (13–17 years) with schizophrenia. Transformed PANSS factors: POS, positive, DIS, disorganized; AA, negative apathy/avolition; DE, negative deficit of expression; HOS, hostility, ANX, anxiety; DEP, depression. Marder PANSS factors: DIS, disorganized; NEG, negative; HOS, hostility.

[a]Pearson's correlation coefficients between the total transformed PANSS factor scores and PANSS total for all subjects and all treatment groups combined.

[b]Pearson's correlation coefficients between PANSS factor scores for positive and each of the indicated symptoms' factor scores. Correlations are presented for change scores to study endpoint (indicated duration). Transformed PANSS factors were calculated using the coefficients of the score matrix (UPSM, supplementary table S1).

17 clinical studies. The transformed PANSS factors yielded low between-factor specificity regardless of the duration of study treatment (6 weeks to 1 year), or other differences in study design or stage of illness. The sum of 7 transformed PANSS factors for each patient at endpoint retained over 90% of the variance of PANSS total (table 4).

Discussion

Applying the UPSM to a pooled sample of 5 placebo-controlled lurasidone clinical trials allowed us to generate UPSM-transformed PANSS factors that exhibited greater specificity than was observed using the standard (Marder[2,3]) PANSS factors in measuring outcomes across symptom domains of schizophrenia.

This work relied on a heuristic observation, namely that the structure of schizophrenia symptoms at baseline appeared somewhat related to the apparent structure of symptom change over time (postbaseline), suggesting that the structure of schizophrenia symptoms might be somewhat invariant to current treatment interventions. Similar clustering at baseline, and by change-over-treatment, indicated to us that specificity of improvements might be determined mathematically by transforming PANSS onto more orthogonal factors that would still correspond well with the known structure of schizophrenia symptoms.

The UPSM-transformed PANSS factors reported here were found to meet three key *criteria*: (1) to have good face validity based on correspondence to the standard

(Marder) PANSS factors; (2) to account for almost all the total variance observed in PANSS total score change; and (3) to exhibit minimal between-factor correlation (high specificity/orthogonality). The transformed PANSS factors correlated well with the standard (Marder) PANSS factors (r = .65–.94), thus indicating that both factors are measuring very similar schizophrenia symptom domains (*criterion #1*). The sum of the 7 transformed PANSS factors retained over 90% of the variance contained in the PANSS total score, thus indicating that there was minimum loss of information related to total symptom severity using the transformed PANSS factors (*criterion #2*). The transformed PANSS factor change scores exhibited markedly reduced between-factor correlations (most r-values <.15) when compared to the between-factor correlations observed with the standard (Marder) PANSS factors (most r-values >.50; *criterion #3*).

In a series of validation analyses, the performance of the UPSM-transformed PANSS factors was examined in 12 additional clinical trials in schizophrenia. The 12 clinical studies spanned a diverse range of patient populations (ages 13–55), durations (6 weeks to 1 year), geographical regions (US, Europe, Asia), and study designs (double-blind, placebo-controlled, and open-label). The results of these validation analyses found that the transformed PANSS factors had similar performance characteristics, with minimal correlation between factors, suggesting that the UPSM transform provides a robust and generalizable method for enhancing the ability of the existing PANSS instrument to measure specific treatment effects across key symptom domains of schizophrenia.

Standard (Marder) PANSS factor scores weight each PANSS item as "0" or "1". Here we generated "refined" PANSS factor score estimates[31] by differentially weighting each PANSS item according to the coefficients in the score matrix. The factor structure in the current analysis was consistent with results from previously reported factor analyses, including our finding that the PANSS negative symptom factor included two subfactors, apathy/avolition and deficit of expression.[32–34] In addition, there is evidence to suggest that these respective negative symptom and depression/anxiety factor subfactors may be subserved by distinct neurocircuitry.[35–37]

Transformed PANSS factors and efficacy

Measuring efficacy (in the pooled 5-study sample) using transformed PANSS factors yielded greater heterogeneity in lurasidone vs placebo effect sizes when compared to effect sizes calculated using standard (Marder) factors. In the current analysis, between-factor correlations on the standard (Marder) PANSS factors were high, especially correlations with the PANSS positive factor (range: r = 0.52–0.74). Such high correlations, commonly characterized as pseudospecificity,[18,19] may result in an overestimate of the effect of treatment on factors that exhibit moderate-to-high correlations with the PANSS positive factor. In contrast, we observed greater differences in lurasidone effect sizes when measuring outcome using transformed PANSS factors. Effect sizes were similar for PANSS positive and hostility factors (for transformed vs Marder), however lurasidone effect sizes were smaller for the three transformed PANSS factors, negative (apathy/ avolition; deficit of expression), disorganized, and depression/anxiety factors. The smaller lurasidone effect sizes were nevertheless statistically significant versus placebo, indicating the presence of specific treatment effects on these 3 domains, independent of improvement in PANSS-positive and -hostility factors. In addition, an analysis of the 12 clinical studies used for cross-validation found greater contrast in effect sizes among symptom domains using the transformed PANSS factors versus the Marder PANSS factors (data not shown).

The availability of orthogonal, minimally correlated measures of severity across key symptom domains in schizophrenia should allow clinicians to more clearly delineate the strengths and weaknesses of available treatments, and may permit selection of antipsychotic drug treatments that have specific (and not simply pseudospecific) efficacy in patients presenting with selected symptom profiles. The availability of valid measures of symptom change, without confounding pseudospecificity, can also facilitate the drug development process, permitting a more accurate characterization of the efficacy of putative new agents in targeting specific symptom domains in patients with psychotic illness.

Limitations

It is uncertain how well the results of the current analysis generalize to clinical (nonresearch) settings, or to more homogeneous patient populations (eg, patients with predominant negative symptoms). PANSS data collected by raters operating under standardized clinical conditions may have influenced the extent of inter-item correlations and pseudospecificity concerns reported here. Examination of additional clinical trial data sets are needed to determine if the UPSM transform identified in supplementary table S1 continues to satisfy validation criteria. Since the objective was to compare 2 different estimates of change in PANSS factors, rather than to describe drug effects per se, we note that the results regarding drug and placebo effects were analyzed as Last Observation Carried Forward and effect sizes may differ with alternative handling of missing observations. Additional statistical limitations include: the factoring of change scores did not distinguish repeated measures within-patients vs between-patient measures, in order to increase statistical confidence in the coefficients of the score matrix. The analysis of PANSS over time (study visits), by varying subgroups (including placebo and active drugs, different

dose levels, across study populations, demographics, geographies), was intended to capture their combined influence on the structure and coefficients of the UPSM transform reported in supplementary table S1.

Conclusions

These results report on an UPSM that can be applied to individual PANSS items to generate transformed PANSS factors that exhibit minimal between-factor correlations while retaining a high degree of correspondence to standard (Marder) PANSS factors. We have separately validated that the specific UPSM transform reported here continues to generate minimal between-factor correlations across a wide variety of different clinical trials in schizophrenia, confirming that the UPSM transform reported in supplementary table S1 provides a potentially robust and generalizable method, using the existing PANSS scale, to measure, with enhanced specificity, treatment effects across key symptom domains of schizophrenia. The transformed PANSS factors and the score matrix reported here provide a more robust understanding of the structure of symptom change in schizophrenia, allow for a clearer understanding of the profile of treatment effects across the symptom domains of schizophrenia, and may provide a useful measurement instrument to evaluate specificity of treatment effects for candidate antipsychotic agents.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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