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Characterization of specific and distinct patient types in clinical trials of acute schizophrenia using an uncorrelated PANSS score matrix transform (UPSM)

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ABSTRACT

Understanding the specificity of symptom change in schizophrenia can facilitate the evaluation antipsychotic efficacy for different symptom domains. Previous work identified a transform of PANSS using an uncorrelated PANSS score matrix (UPSM) to reduce pseudospecificity among symptom domains during clinical trials of schizophrenia. Here we used UPSM-transformed factor scores to identify 5 distinct patient types, each having elevated and specific severity among each of 5 symptom domains. Subjects from placebo-controlled clinical trials of acute schizophrenia were clustered (baseline) and classified (post-baseline) by a machine-learning algorithm. At baseline, all 5 patient types were similar in PANSS total score. Post-baseline, subjects' memberships among the 5 UPSM patient types were relatively stable over treatment duration and were relatively insensitive to overall improvements in symptoms, in contrast to other methods based on untransformed PANSS items. Using UPSM-transformed PANSS, drug treatment effect sizes versus placebo were doubly-dissociated for specificity across symptom domains and within specific patient types. This approach illustrates how broader clinical trial populations can nevertheless be utilized to characterize the specificity of new mechanisms across the dimensions of schizophrenia psychopathology.

1. Introduction

The diagnosis of schizophrenia is associated with a high degree of symptom heterogeneity. The heterogeneity of symptoms, when viewed by factor analytic approaches(Emsley et al., 2003; Lindenmayer et al., 1995; Marder et al., 1997; Wallwork et al., 2012), have consistently identified 5 factors, the first 3 of which approximately map onto the current DSM-5 core criteria (positive symptoms, negative symptoms, disorganized thinking) plus the 2 associated symptom domains of hostility/excitement, and depression/anxiety.

Decades of treatment research and clinical experience suggest that currently available antipsychotic medications are likely not comparably effective across all 5 symptom domains (Leucht et al., 2009). However, the ability to detect differential, domain-specific treatment effects is not possible because of the extent to which PANSS factors, the gold standard for measuring efficacy in schizophrenia, are correlated with each other (Citrome et al., 2011; Loebel et al., 2015; Marder et al., 1997; Trampush et al., 2015). These measurement issues, sometimes referred to as pseudospecificity (Leber, 2002), have hampered efforts to accurately characterize the effects of a given treatment on a specific symptom domain independent of correlated improvements (or impairments) in other domains (Laughren and Levin, 2011). Also impeded is the ability to determine whether new drugs in development, having mechanisms of action distinct from dopamine blockade, have improved domain-specific efficacy (Koblan et al., 2020).

Although negative symptoms are considered core to the disorder, it remains unclear to what extent negative symptoms are specifically treated with current antipsychotics (Fusar-Poli et al., 2015; Krause et al., 2018; Leucht et al., 2017). In trials of acute schizophrenia, any improvements in negative symptoms may be secondary to overall improvement or to improvement in other domains (Carpenter and Buchanan, 2017; Kirkpatrick et al., 2006). Clinical trials of novel compounds not acting via blockade of dopamine D2 receptors have been designed to target more-specific patient populations in an attempt to address specificity of improvements. Such designs rely on trial populations and stringent patient selection criteria to create

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more-homogenous subgroups of schizophrenia, selecting patients who present with persistence, prominence, and/or predominance of negative symptoms (Davidson et al., 2017; Nemeth et al., 2017; Stauffer et al., 2012; Umbricht et al., 2014). However, it is unclear whether studies in such sub-populations can solve the problem of pseudospecificity (Marder et al., 2013), given the complexities of restricting criteria for negative symptoms prior to demonstrating specific benefits of treatment (Dunayevich et al., 2014). In contrast, diagnostic concepts of schizophrenia have moved away from traditional subtypes due to a lack of diagnostic reliability, difficulty in distinguishing between subtypes, and uncertain value in predicting treatment response (Andreasen et al., 1997; Bartko et al., 1981; Braff et al., 2013; Mattila et al., 2015). New methodological approaches are needed to better characterize efficacy of current and future antipsychotic drug mechanisms within symptom domains and among patient types.

We propose analyzing existing clinical trial databases to unify dimensional (factor analytic) and typological (distinct subtypes) constructs for more-accurate depictions of drug efficacy, and to apply these to the clinical development and differentiation of novel therapeutics. Previously we have described the use of an Uncorrelated PANSS Score Matrix (UPSM) transform of the PANSS scale (Hopkins et al., 2017, 2018) to describe change scores which have minimal correlations to each other, but still retain a high degree of correspondence with standard PANSS factors. Standard PANSS factors, on the other hand, demonstrate a high degree of correlations to each other, hindering interpretation of the specificity of improvements in any one symptom domain independently from overall improvements (pseudospecificity). The application of UPSM was validated across 12 clinical trials independent of the data from which UPSM was derived (Hopkins et al., 2018) using PANSS data collected in other drug development programs, including non-D2 compounds (Mahableshwarkar AR, 2017).

Here we extend this work, showing how use of the UPSM-transformed PANSS scores identified 5 distinct patient subtypes characterized by prominent severity along each of the 5 dimensions of schizophrenia. We used a machine-learning algorithm trained on the baseline UPSM-transformed PANSS factor scores to identify patient-type membership post-baseline. We summarize here results of analyses showing that the 5 patient types are relatively stable over time. We also provide data suggesting that these patient types are associated with distinct clinical characteristics and treatment responses.

2. Methods

The analysis dataset was a sample of 1710 patients 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. An analysis of this same clinical sample identified (Hopkins et al., 2018) an Uncorrelated PANSS Score Matrix (UPSM) based on change scores post-baseline. Here the UPSM transform was applied to absolute PANSS scores to develop a patient type classifier. Application of UPSM to PANSS scores directly (rather than change scores) was described previously (Hopkins et al., 2017). Rating scales other than PANSS were used to validate the relative symptom severities among the UPSM patient types, including depressive symptoms (MADRS scores available on $N = 1404$ subjects at baseline), negative symptoms (NSA-16, $N = 465$ subjects), neuropsychological cognition (CogState, $N = 444$ subjects), and functional cognition (UPSA-B, $N = 467$ subjects). The utility of the UPSM patient-type classifier was validated in patients from studies independent of the patients used to derive the classifier, and independent of the patient sample used to derive UPSM. Two 12-month studies (Studies NCT00789698 and NCT00641745) were used to evaluate the stability of patient-types over longer-term treatment periods. Study NCT00789698 included subjects ($N = 292$) treated with lurasidone or quetiapine XR or placebo (Loebel et al., 2013). Study NCT00641745 included subjects ($N = 629$) treated with lurasidone or risperidone (Citrome et al., 2012).

Subjects at baseline were clustered into 5 patient types with the intent to collect subjects presenting with high specificity for each of the 5 domains of schizophrenia. The scores for each subject's 30 PANSS items were UPSM-transformed into 7 UPSM factor scores. The 7 UPSM factor scores were: positive (POS), hostility (HOS), disorganized (DIS), negative apathy avolition (NAA), negative deficit of expression (NDE), anxiety (ANX), and depression (DEP). Subjects were clustered by k-means (MATLAB version) based on their 7 UPSM factor scores at baseline. The distinctness of the 5 UPSM clusters was evaluated using silhouette values for each subject as calculated (MATLAB) using a Euclidean distance metric to compare the separation of subjects to their own cluster, when compared to their separation to subjects in other clusters. The silhouette value for the ith subject, Si, is defined as $Si = (bi - ai) / \max(ai, bi)$, where ai is the average distance from the ith subject to the other subjects in the same cluster as i, and bi is the minimum average distance from the ith subject to subjects in a different cluster, minimized over clusters. The validity of the 5 clusters generated by k-means was evaluated against an alternate clustering method (Ward's). The 5 clusters generated by the 2 different algorithms were compared using the Rand Index, which is a measure of the relative similarity between clustering outcomes (Dollfus et al., 1996; Rand, 1971). A similar pattern of clustering emerged regardless of the algorithm used for clustering (the Rand Index was 0.75 when comparing clustering assignments by k-means versus Ward's), supporting further analyses of the 5 distinct types of schizophrenia patients as identified from the 7 UPSM factor scores.

A classification algorithm was developed to assign subjects post-baseline into each of the 5 patient types based on their post-baseline UPSM factor scores, without having to re-cluster new observations. A machine learning classifier (SVM in MATLAB) of UPSM factor scores for each subject were used to assign the patient type based on proximity to each pre-identified cluster centers and boundaries. The accuracy of the SVM classifier on the training set (baseline assessments) was over 97% for correct assignment of cluster membership. Euclidean distances were calculated in a 7-dimensional space using the 7 UPSM factor scores. The boundaries among the 5 patient-type clusters were determined in 7-dimensional Euclidean space

Baseline demographic and geographic variables by patient type were summarized with descriptive statistics. Treatment responses within each cluster were estimated by descriptive statistics and using last observation carried forward (LOCF).

The stability of patient type memberships over time were descriptively summarized using SANKEY plots (Google Plot Version). Rand index (Rand, 1971), a measure of the similarity between two data clusters, was adapted here to quantify the stability of subjects within patient-types between successive visits.

A MATLAB executable (available in Supplementary Material online) is available to calculate UPSM factor scores and assign patient type using subject-level PANSS item scores.

3. Results

3.1. Distinctness of patient types

At baseline, acutely exacerbated schizophrenia subjects in the pooled sample ($N = 1710$) were clustered into 5 distinct profiles of UPSM-transformed PANSS factor scores (Prominently Positive, Prominently Hostile, Prominently Disorganized, Prominently Affective, and Prominently Negative) based on their profiles of severity across the 7 UPSM-transformed factor scores (see upper panels of UPSM profiles in Fig. 1). The histograms of silhouette values indicate that the majority of subjects were well-matched to their respective cluster centers, and poorly matched to the other cluster centers (lower panels in Fig. 1). Severity of symptoms were equivalent betweeen the clusters. Mean PANSS total scores and mean CGI-S scores were similar among the 5 baseline clusters, indicating that total symptom severity did not

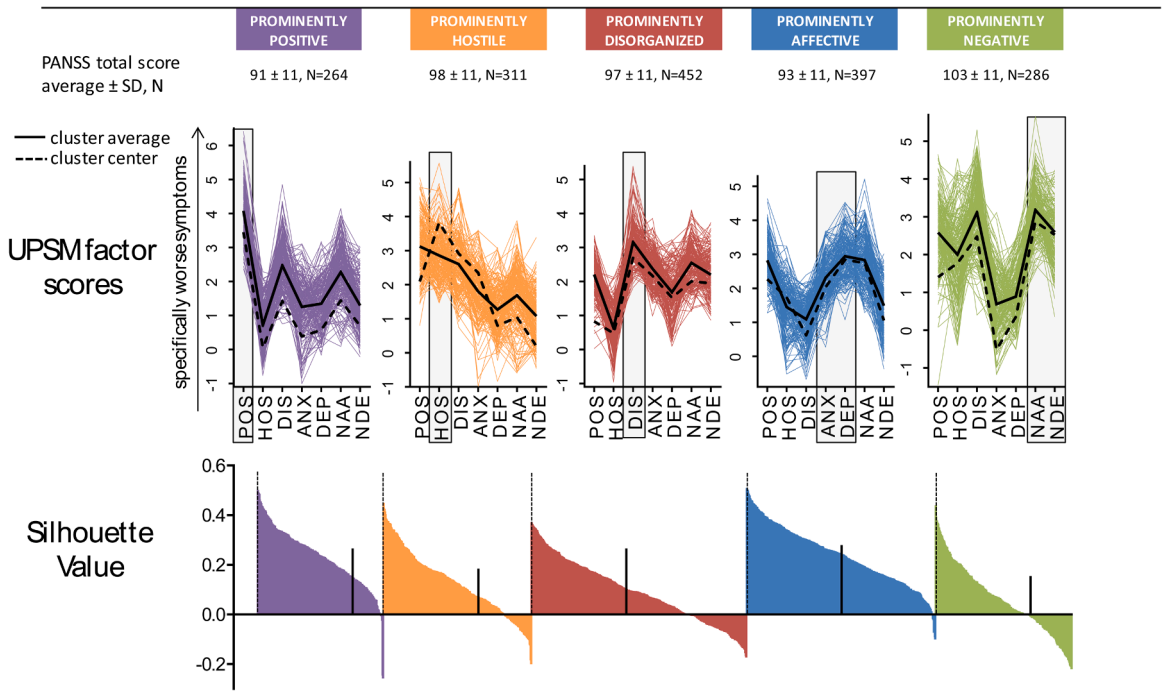

Fig. 1. UPSM factor scores at baseline cluster into 5 distinct patient types. Upper panels show the profiles of individual subjects' UPSM factor (y-axis). Each colored line is an individual subject's UPSM factor scores. The first 200 subjects in each cluster is shown in upper panels. The subject corresponding to the cluster average (solid line) and the subject corresponding to the cluster center (dashed line) is shown for each cluster. Lower panels show the histograms of all ($N = 1710$) subjects' silhouette values in each patient type, as ranked by proximity (Euclidean distance) to the cluster center (dashed line). Higher silhouette values (y-axis) indicate that a subject's UPSM profile is both well-matched within its own cluster and poorly-matched to neighboring clusters.

contribute substantially to differentiating the patient types (Table 1). Depressive symptoms assessed with MADRS were greater in the affective type (mean 16) than in any other patient type and greater than the overall population (mean 11 ± 7 sd, $N = 1404$). The affective patient type appeared to have higher levels of cognitive performance (mean scores on cognitive battery CogState) and a higher level of cognitive functioning (mean scores UPSA-B). Mean scores of negative symptoms (NSA-16) were higher in the negative patient type, and mean scores of cognitive functioning and performance were also lower in this patient type. Clinical sites in Eastern Europe more commonly enrolled the disorganized patient type, a patient type that had a higher mean rate of hospitalization (Table 2). Clinical sites in the USA more commonly enrolled the affective patient type, which had a greater proportion of African ancestry, had a lower mean rate of hospitalization, and were heavier and older than other patient types (Table 2). Clinical sites outside of USA and Eastern Europe more commonly enrolled the

Table 1
Acute schizophrenia patient types at baseline.

	PROMINENT POSITIVE	PROMINENT HOSTILE	PROMINENT DISORGANIZED	PROMINENT AFFECTIVE	PROMINENT NEGATIVE	ALL SUBJECTS			
Number of subjects	264	311	452	397	286	AVG		SD	N
PANSS Total score	91	98	97	93	103	96	±	11	1710
UPSM POSITIVE	3.9	3.1	2.4	2.8	2.6	2.9	±	0.9	1710
UPSM HOSTILITY	0.7	2.6	0.7	1.4	1.9	1.4	±	1.1	1710
UPSM DISORGANIZED	2.4	2.6	3	1.4	3.1	2.5	±	1	1710
UPSM ANXIETY	1.4	1.8	2.3	2.3	0.8	1.8	±	0.9	1710
UPSM DEPRESSION	1.4	1.3	1.7	2.7	0.9	1.7	±	1	1710
UPSM APATHY AVOLITION	2.3	1.8	2.5	2.7	3.1	2.5	±	0.9	1710
UPSM DEFICIT OF EXPRESSION	1.3	1.2	2.1	1.6	2.5	1.8	±	0.9	1710
MARDER POSITIVE	31	31	28	28	30	29	±	4.3	1710
MARDER HOSTILITY	8	15	9	10	12	11	±	3.4	1710
MARDER DISORGANIZED	21	22	24	18	25	22	±	4.4	1710
MARDER DEPRESSION	10	11	12	14	8	11	±	3.2	1710
MARDER NEGATIVE	20	19	24	22	28	23	±	4.9	1710
NSA Total score	48	46	56	48	61	53	±	13	465
MADRS TOTAL SCORE	8.2	9.8	12	16	9.2	11	±	7	1404
CGI-S	5	5	5	5	5	5	±	1	1710
UPSA Total score	64	64	67	72	58	65	±	21	467
COGSTATE Composite score	−1.2	−1.3	−1.1	−0.7	−1.8	−1.2	±	1.1	444
Age(y)	38.5	37	38.2	41.3	35.5	38.3	±	10.6	1710
Weight (kg)	76.3	72.9	77.3	84.4	69.4	76.2	±	18.8	1404
BMI	26.2	25.5	26.1	28	24.3	26.1	±	5.4	1404
Number of hospitalizations	2.6	2.5	3.3	3	2.4	2.8	±	1.5	1404
Duration of illness (y)	14.2	12.1	13.3	16.3	11.5	13.5	±	10.2	1404
Rate of hospitalizations (per yr)	0.33	0.28	0.45	0.31	0.33	0.35	±	0.55	1404

Table 2
Acute schizophrenia patient sub-types at baseline (%).

	PROMINENT POSITIVE	PROMINENT HOSTILE	PROMINENT DISORGANIZED	PROMINENT AFFECTIVE	PROMINENT NEGATIVE	All
Female	31	27	30	23	27	27
Male	70	73	70	77	73	73
White	39	41	64	39	35	45
Black or African American	33	26	28	53	24	33
Asian	22	30	4	5	34	17
Other	6	4	4	3	7	4
USA	58	44	52	90	34	57
Eastern Europe	15	20	36	4	24	20
Rest of world	27	35	12	6	42	22

negative type (Table 2). Marder PANSS factor scores, when clustered by similar methods, placed subjects into clusters of low and high PANSS total rather than in clusters with distinct profiles of symptoms within symptom domains (Supplemental Figure 1). The assignments were distinct from the clusters based on UPSM (adjusted Rand Index of 0.14). Post-baseline assignments to Marder clusters indicated that the low-severity type grew in membership and the high-severity type shrank in membership, as PANSS total scores tended to decrease over time (Supplemental Figure 2).

3.2. Stability of patient types

Membership of subjects among the 5 UPSM patient-type classifications was relatively stable over time (Fig. 2a). For example, between any 2 sequential PANSS assessments during a 6-week acute schizophrenia trial, patient type classification remained unchanged on average 69% of the time ($N = 1710$), even in the context of overall changes (improvements) in PANSS total score. Between baseline and endpoint, there was an overall similarity of membership among patient types, as indicated by a relatively high Rand Index of 0.70, indicating a high degree of similarity in classification between visits. A Rand index $\leq$ 0.3 attributes similar clustering by chance and rand index >= 0.7 attributes similar clustering due to inherent information in data. Over the 6 weeks of treatment duration, 33% of subjects at endpoint remaining unchanged relative to their baseline patient type. In longer-term clinical trials, patient-type membership was similarly stable. In 2 separate 12-month clinical trials of chronic schizophrenia (Studies NCT00789698 and NCT00641745), after 12 months of study participation, 50% and 41% of the subjects were classified the same as their baseline patient type, respectively, and combining the studies, at the end of 12 months, 44% of the subjects remained in the same cluster as baseline, with a Rand Index of 0.66. Rand Index between successive visits for all 12 months is between 0.72 – 0.76 that shows long-term stability of this patient type classification. The Rand Index tended to increase between successive visits over both the pool of 6-week studies (Fig. 2a) as well as in the pool of 12-month studies (Fig. 2b), indicating that patient type classification stabilizes further over time with fewer patients changing membership.

3.3. Double-dissociation of treatment effects using patient types

Using UPSM, drug treatment effects were doubly-dissociated for specificity across symptom domains (dimensional) and for specificity within patient types (typological). Effect size estimates for pooled lurasidone-treated subjects for baseline-to-endpoint change, difference from placebo, were used to compare treatment responses (Fig. 3) across symptom dimensions (rows) and among patient types (columns). In terms of symptom dimensions, positive symptoms (UPSM-POS) improved in patient types who were prominently positive (e.s. 0.33), hostile (e.s. 0.37), disorganized (e.s. 0.43) and negative (0.47). Hostile symptoms (UPSM-HOS) improved in patient types who were prominently hostile (e.s. 0.29), disorganized (e.s. 0.26), and negative (e.s. 0.34). Disorganized symptoms (UPSM-DIS) improved in patient types who were prominently disorganized (e.s. 0.32) and negative (e.s. 0.31). Negative apathy/avolition symptoms (UPSM-NAA) only improved in patient types who were prominently positive (e.s. 0.57). Negative symptoms of deficit of expression (UPSM-NDE) did not appear to improve in any patient type, consistent with a lack of effect in the overall population.

In the total population (all patient types), the overall effect size for drug-related improvement in PANSS total was 0.46 (bottom right, Fig. 3). Disorganized types demonstrated the largest PANSS total effect size (0.55), and affective types the smallest (0.38). The overall improvement in symptoms in the negative patient types (PANSS total e.s. 0.44) was without any specific drug effect on negative symptoms (UPSM-NAA e.s. 0.05; UPSM-NDE e.s. 0.00). Rather, in these negative patient types, specific drug effects were apparent on positive (e.s. 0.47), hostile (e.s. 0.34), and disorganized (e.s. 0.31) symptoms. In other patient types, specific drug effects were detected in the same dimension of the symptom domain defining the patient type. For example, in hostile patient types there were drug-related improvements specific to positive, hostility and depression symptoms. In disorganized patient types, there were drug-related improvements specific to disorganized, positive, hostility and anxiety symptoms. In affective patient types the UPSM factor score effect sizes were all below 0.3, consistent with the lowest overall effect size (PANSS total) in this patient type.

4. Discussion

These results describe an approach to characterizing the specificity of a drug treatment effect across the symptom domains of schizophrenia, where drug treatment effect sizes on total symptoms in the broad population can be doubly-dissociated by symptom-specific effect sizes (dimensional) and among distinct patient types (typological). This work uncovers the presence and persistence of distinct patient types using UPSM factor scores, which are uncorrelated to the overall symptom changes that typically occur post-baseline in acute schizophrenia drug treatment trials. Representing schizophrenia symptoms along UPSM factors allowed for classification of individual patients by their relative severity among the 5 dimensions of schizophrenia psychopathology, uncorrelated from overall symptom severity. Since UPSM-patient type membership was relatively independent of total symptom severity, as PANSS total scores improved, patients tended to remain stable in their classification over treatment duration. In contrast, the now-abandoned traditional subtypes of schizophrenia, based on clinical features, are not distinguishable symptomatically and not stable longitudinally (Braff et al., 2013). The classification of UPSM patient types is thus a prospective mathematical classification for any new patient having any new assessment of PANSS, and is independent of the clustering and the data that was used to derive the subtypes.

That the UPSM patient types described here were relatively independent of total symptom severities was in marked contrast to other methods of identifying subtypes. Clustering of traditional PANSS factors or the scores of other assessment instruments is sensitive to total symptom severity. For example, clustering Marder PANSS factors

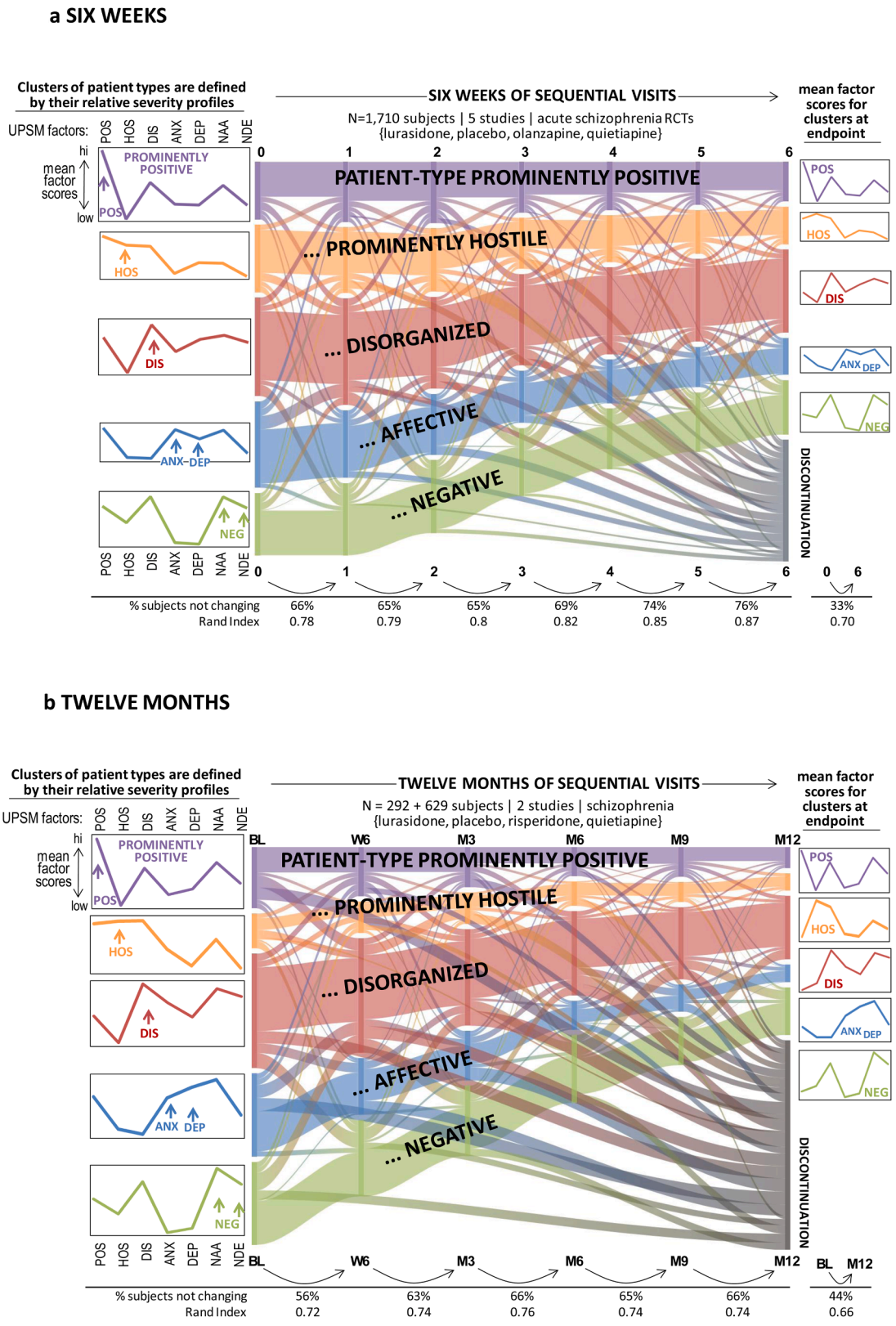

Fig. 2. Patient-type classification over treatment duration. Each of the 5 UPSM-patient types at baseline are represented for each cluster (panels left column) with line plot for the 7 UPSM factor scores. The Sankey Plot depicts the portion of patients in each cluster that remain or change membership (or discontinue) at each of the sequential weekly visits. In the table below each panel, the percent of subjects not changing UPSM-patient type membership, and the corresponding Rand Index, are shown for each between-visit and between baseline and endpoint. The right column of panels shows the line plots for the UPSM factor scores for each UPSM-patient type at endpoint.

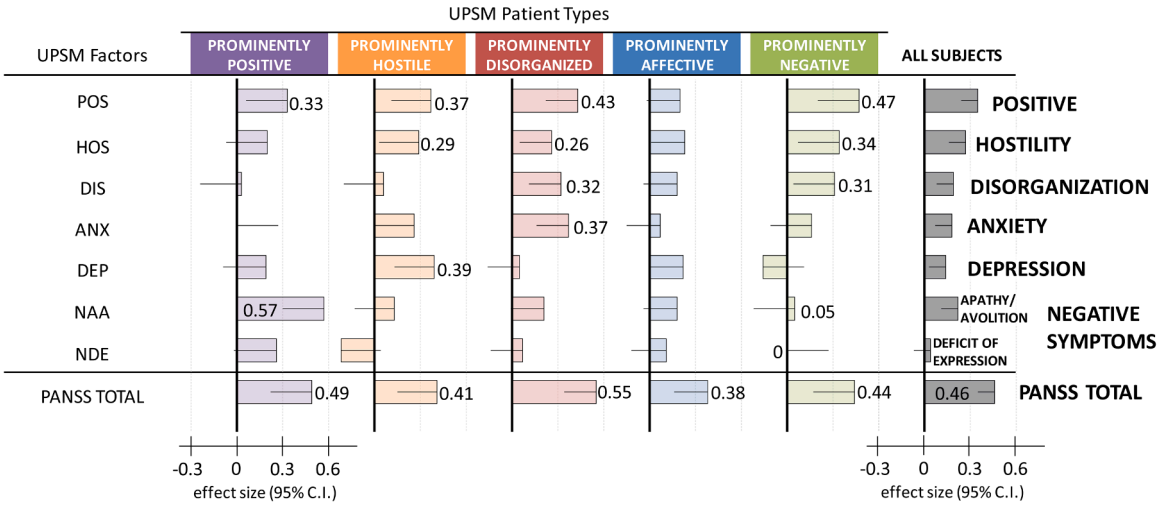

Fig. 3. Effect size estimates for pooled lurasidone-treated subjects' baseline-to-endpoint change, difference from placebo ($N = 1710$, LOCF).

produced clusters which were largely determined by PANSS total scores (not specific), without meaningful separation (not distinct), and with memberships changing over treatment duration (not stable). A continuum of severity in schizophrenia symptoms can mislead classification systems attempting to account for apparent heterogeneity (Goldberg and Weinberger, 1995). UPSM clusters, in contrast, did not rely on outliers or extreme cases to define patient types. The silhouette values for the UPSM clusters spanned most of the cluster and were distinct to each cluster.

The identity of each UPSM-defined patient types was face-valid with assessments made on scales other than PANSS, such as MADRS and NSA-16 for depressive and negative symptoms, respectively. The distribution of UPSM patient types appeared dependent on geography, an effect which was consistent between different trials. Demographic variables such as age, BMI, ancestry, and psychiatric history varied among the patient types. Cognitive function also tended to differ between patient types. UPSM-defined patients remained classified into their respective patient type during longer (12-months) treatments. Taken together, these results suggest that UPSM-defined patient types may provide a novel approach to analyze trials dedicated to understanding the neurobiological or genetic contributions to schizophrenia psychopathology.

The PANSS scale was developed to provide more standardization across a broader array of symptoms (Kay et al., 1987) and to support dimensional factor-analytic analyses (Kay and Sevy, 1990). The inclusion of standardized PANSS assessments in industry-sponsored efficacy trials have generated large databases. For example, the database of lurasidone clinical development trials combined contains approximately 60,000 PANSS assessments on roughly 6000 unique patients (Sunovion Pharmaceuticals). The large number of standardized PANSS assessments has allowed this UPSM analysis to combine dimensional (factor analytic) and typological (distinct subtypes) for more-accurate depictions of drug efficacy. We propose that analysis methods such as these can be used to describe the relative efficacy profile of new non-D2 treatments in schizophrenia (Dedic et al., 2019a, 2019b; Koblan et al., 2020), with specificity along symptom change and among patient types in a broader population.

Recently data-driven approaches (Grisanzio et al., 2018; Ivleva et al., 2017) have attempted to connect symptoms of mental disorders to underlying neurobehavioral dimensions with focus on objective, performance-based and neuroimaging-based measures. We propose that UPSM-defined patient types allow for a novel use of PANSS in such data-driven approaches.

5. Limitations

The UPSM patient types identified in this work relied on large numbers of PANSS assessments, whereas the applicability of UPSM patient type classification at an individual patient level is uncertain without prospective clinical trials. Likewise the demographic variables associated with each patient type were only analyzed by descriptive statistics, due to the post-hoc and pooled nature of the analysis. Future clinical trials incorporating analyses by UPSM patient type will help to demonstrate specific effects of novel treatments, or to demonstrate the specificity of any genetic or neurobiological contributions to schizophrenia psychopathology.

CRediT authorship contribution statement

Seth C. Hopkins: Conceptualization, Supervision, Visualization. **Ajay Ogirala:** Formal analysis, Methodology, Data curation. **Antony Loebel:** Investigation, Resources, Writing - review & editing. **Kenneth S. Koblan:** Conceptualization, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors are employees of Sunovion Pharmaceuticals and have declared that there are no conflicts of interest in relation to the subject of this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.113569.

References

Andreasen, N.C., Flaum, M., Schultz, S., Duzyurek, S., Miller, D., 1997. Diagnosis, methodology and subtypes of schizophrenia. Neuropsychobiology 35 (2), 61–63. https://doi.org/10.1159/000119390.

Bartko, J.J., Carpenter Jr., W.T., Strauss, J.S., 1981. Statistical basis for exploring schizophrenia. Am. J. Psychiatry 138 (7), 941–947. https://doi.org/10.1176/ajp.138.7.941.

Braff, D.L., Ryan, J., Rissling, A.J., Carpenter, W.T., 2013. Lack of use in the literature from the last 20 years supports dropping traditional schizophrenia subtypes from DSM-5 and ICD-11. Schizophr. Bull. 39 (4), 751–753. https://doi.org/10.1093/schbul/sbt068.

Carpenter Jr., W.T., Buchanan, R.W., 2017. Negative symptom therapeutics. Schizophr. Bull. 43 (4), 681–682. https://doi.org/10.1093/schbul/sbx054.

Citrome, L., Cucchiaro, J., Sarma, K., Phillips, D., Silva, R., Tsuchiya, S., Loebel, A., 2012. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month,

double-blind, active-controlled study. Int. Clin. Psychopharmacol. 27 (3), 165–176. https://doi.org/10.1097/YIC.0b013e32835281ef.
Citrome, L., Meng, X., Hochfeld, M., 2011. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. Schizophr. Res. 131 (1–3), 75–81. https://doi.org/10.1016/j.schres.2011.05.018.
Davidson, M., Saoud, J., Staner, C., Noel, N., Luthringer, E., Werner, S., Luthringer, R., 2017. Efficacy and safety of MIN-101: a 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. Am. J. Psychiatry 174 (12), 1195–1202. https://doi.org/10.1176/appi.ajp.2017.17010122.
Dedic, N., Jones, P.G., Hopkins, S.C., Lew, R., Shao, L., Campbell, J.E., Koblan, K., 2019a. SEP-363856, a novel psychotropic agent with a unique, Non-D2 receptor mechanism of action. J. Pharmacol. Exp. Ther. https://doi.org/10.1124/jpet.119.260281.
Dedic, N., Jones, P.G., Hopkins, S.C., Lew, R., Shao, L., Campbell, J.E., Koblan, K.S., 2019b. SEP-363856, a novel psychotropic agent with a unique, Non-D2 receptor mechanism of action. J. Pharmacol. Exp. Ther. 371 (1), 1–14. https://doi.org/10.1124/jpet.119.260281.
Dollfus, S., Everitt, B., Ribeyre, J.M., Assouly-Besse, F., Sharp, C., Petit, M., 1996. Identifying subtypes of schizophrenia by cluster analyses. Schizophr. Bull. 22 (3), 545–555. https://doi.org/10.1093/schbul/22.3.545.
Dunayevich, E., Chen, C.Y., Marder, S.R., Rabinowitz, J., 2014. Restrictive symptomatic inclusion criteria create barriers to clinical research in schizophrenia negative symptoms: an analysis of the CATIE dataset. Eur. Neuropsychopharmacol. 24 (10), 1615–1621. https://doi.org/10.1016/j.euroneuro.2014.08.004.
Emsley, R., Rabinowitz, J., Torreman, M., 2003. The factor structure for the positive and negative syndrome scale (PANSS) in recent-onset psychosis. Schizophr. Res. 61 (1), 47–57.
Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., McGuire, P., 2015. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizophr. Bull. 41 (4), 892–899. https://doi.org/10.1093/schbul/sbu170.
Goldberg, T.E., Weinberger, D.R., 1995. A case against subtyping in schizophrenia. Schizophr. Res. 17 (2), 147–152.
Grisanzio, K.A., Goldstein-Piekarski, A.N., Wang, M.Y., Rashed Ahmed, A.P., Samara, Z., Williams, L.M., 2018. Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, anxiety, and trauma disorders. JAMA Psychiatry 75 (2), 201–209. https://doi.org/10.1001/jamapsychiatry.2017.3951.
Hopkins, S.C., Ogirala, A., Loebel, A., Koblan, K.S., 2017. Understanding antipsychotic drug treatment effects: a novel method to reduce pseudospecificity of the positive and negative syndrome scale (PANSS) factors. Innov. Clin. Neurosci. 14 (11–12), 54–58.
Hopkins, S.C., Ogirala, A., Loebel, A., Koblan, K.S., 2018. Transformed PANSS factors intended to reduce pseudospecificity among symptom domains and enhance understanding of symptom change in antipsychotic-treated patients with schizophrenia. Schizophr. Bull. 44 (3), 593–602. https://doi.org/10.1093/schbul/sbx101.
Ivleva, E.I., Clementz, B.A., Dutcher, A.M., Arnold, S.J.M., Jeon-Slaughter, H., Aslan, S., Tamminga, C.A., 2017. Brain structure biomarkers in the psychosis biotypes: findings from the bipolar-schizophrenia network for intermediate phenotypes. Biol. Psychiatry 82 (1), 26–39. https://doi.org/10.1016/j.biopsych.2016.08.030.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276. https://doi.org/10.1093/schbul/13.2.261.
Kay, S.R., Sevy, S., 1990. Pyramidical model of schizophrenia. Schizophr. Bull. 16 (3), 537–545. https://doi.org/10.1093/schbul/16.3.537.
Kirkpatrick, B., Fenton, W.S., Carpenter Jr., W.T., Marder, S.R., 2006. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 32 (2), 214–219. https://doi.org/10.1093/schbul/sbj053.
Koblan, K.S., Kent, J., Hopkins, S.C., Krystal, J.H., Cheng, H., Goldman, R., Loebel, A., 2020. A Non-D2-receptor-binding drug for the treatment of schizophrenia. N Engl. J. Med. 382 (16), 1497–1506. https://doi.org/10.1056/NEJMoa1911772.
Krause, M., Zhu, Y., Huhn, M., Schneider-Thoma, J., Bighelli, I., Nikolakopoulou, A., Leucht, S., 2018. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur. Arch. Psychiatry Clin. Neurosci. 268 (7), 625–639. https://doi.org/10.1007/s00406-018-0869-3.
Laughren, T., Levin, R., 2011. Food and drug administration commentary on methodological issues in negative symptom trials. Schizophr. Bull. 37 (2), 255–256. https://doi.org/10.1093/schbul/sbq162.
Leber, P., 2002. Regulatory issues. Eds.. In: Kenneth L. Davis, D.C., Coyle, Joseph T., Nemeroff, C. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. American College of Neuropsychopharmacology.
Leucht, S., Arbter, D., Engel, R.R., Kissling, W., Davis, J.M., 2009. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol. Psychiatry 14 (4), 429–447. https://doi.org/10.1038/sj.mp.4002136.
Leucht, S., Leucht, C., Huhn, M., Chaimani, A., Mavridis, D., Helfer, B., Davis, J.M., 2017. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. Am. J. Psychiatry 174 (10), 927–942. https://doi.org/10.1176/appi.ajp.2017.16121358.
Lindenmayer, J.P., Grochowski, S., Hyman, R.B., 1995. Five factor model of schizophrenia: replication across samples. Schizophr. Res. 14 (3), 229–234.
Loebel, A., Cucchiaro, J., Silva, R., Mao, Y., Xu, J., Pikalov, A., Marder, S.R., 2015. Efficacy of lurasidone across five symptom dimensions of schizophrenia: pooled analysis of short-term, placebo-controlled studies. Eur. Psychiatry 30 (1), 26–31. https://doi.org/10.1016/j.eurpsy.2014.08.001.
Loebel, A., Cucchiaro, J., Xu, J., Sarma, K., Pikalov, A., Kane, J.M., 2013. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, noninferiority study. Schizophr. Res. 147 (1), 95–102. https://doi.org/10.1016/j.schres.2013.03.013.
Mahableshwarkar AR, O.F., Marek, T.A., 2017. Replication of a statistical method to reduce pseudospecificity and enhance understanding of score changes among PANSS factors. Post. Present. 2017 Int. Soc. CNS Clin. Trials Methodol.
Marder, S.R., Alphs, L., Anghelescu, I.G., Arango, C., Barnes, T.R., Caers, I., Rabinowitz, J., 2013. Issues and perspectives in designing clinical trials for negative symptoms in schizophrenia. Schizophr. Res. 150 (2–3), 328–333. https://doi.org/10.1016/j.schres.2013.07.058.
Marder, S.R., Davis, J.M., Chouinard, G., 1997. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J. Clin. Psychiatry 58 (12), 538–546.
Mattila, T., Koeter, M., Wohlfarth, T., Storosum, J., van den Brink, W., de Haan, L., Denys, D., 2015. Impact of DSM-5 changes on the diagnosis and acute treatment of schizophrenia. Schizophr. Bull. 41 (3), 637–643. https://doi.org/10.1093/schbul/sbu172.
Nemeth, G., Laszlovszky, I., Czobor, P., Szalai, E., Szatmari, B., Harsanyi, J., Fleischhacker, W.W., 2017. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet 389 (10074), 1103–1113. https://doi.org/10.1016/s0140-6736(17)30060-0.
Rand, W.M., 1971. Objective criteria for the evaluation of clustering methods. J. Am. Stat. Assoc. 66 (336), 846–850. https://doi.org/10.1080/01621459.1971.10482356.
Stauffer, V.L., Song, G., Kinon, B.J., Ascher-Svanum, H., Chen, L., Feldman, P.D., Conley, R.R., 2012. Responses to antipsychotic therapy among patients with schizophrenia or schizoaffective disorder and either predominant or prominent negative symptoms. Schizophr. Res. 134 (2–3), 195–201. https://doi.org/10.1016/j.schres.2011.09.028.
Trampush, J.W., Lencz, T., DeRosse, P., John, M., Gallego, J.A., Petrides, G., Malhotra, A. K., 2015. Relationship of cognition to clinical response in first-episode schizophrenia spectrum disorders. Schizophr. Bull. 41 (6), 1237–1247. https://doi.org/10.1093/schbul/sbv120.
Umbricht, D., Alberati, D., Martin-Facklam, M., Borroni, E., Youssef, E.A., Ostland, M., Santarelli, L., 2014. Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized, double-blind, proof-of-concept study. JAMA Psychiatry 71 (6), 637–646. https://doi.org/10.1001/jamapsychiatry.2014.163.
Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. Schizophr. Res. 137 (1–3), 246–250. https://doi.org/10.1016/j.schres.2012.01.031.