

PANSS Negative Symptom Dimensions Across Geographical Regions: Implications for Social, Linguistic and Cultural Consistency

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METHODOLOGICAL QUESTION

Recognizing the discrete dimensions that underlie negative symptoms in schizophrenia and how these dimensions are conceptualized across geographical regions may result in better understanding and treatment. The methodological questions to be answered are 1) Will the expressive and experiential dimensions of the PANSS vary over 15 geographical regions and will the item ratings defining each dimension manifest similar reliability across these regions? 2) In large multi-center, international trials where data are combined, which of the two dimensions are disposed to social, linguistic and cultural inconsistency?

INTRODUCTION

The expressive-experiential distinction has been shown to have vast importance in relation to functional outcomes in schizophrenia. Many psychometric measurements, especially in psychiatry, have items that might perform differently with diverse groups.

Studies have shown the PANSS may not be equivalently rated across counties and cultures, suggesting regional differences in both symptom expression and rater judgment of symptom severity. Items that perform in markedly different ways across demographic, regional, cultural, or clinical severity characteristics may not offer valid representations of the target construct. The presence of bias in ratings and the impact of symptoms on overall functioning is of interest.

METHODS

Sample

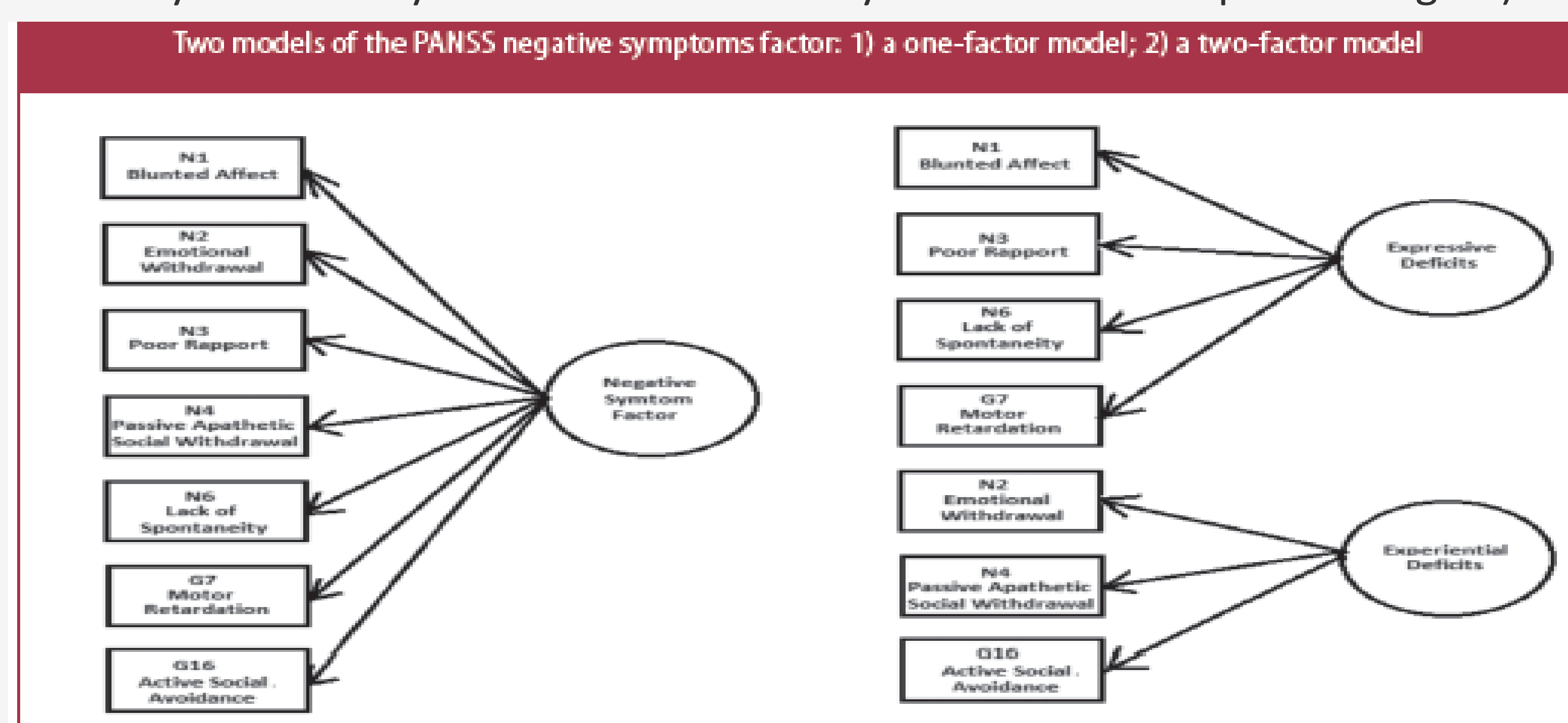
Analysis included baseline PANSS scores from 6,889 subjects enrolled between 1992 and 2005 in one of 16 randomized, double-blind clinical trials.

Statistical Analysis

Step 1: We conducted an exploratory factor analysis (EFA) and a confirmatory factor analysis to identify the sub-factors of Negative symptoms.

Step 2: Three criteria were used to flag items as differentially functioning: 1) significant chi-square ($p \leq 0.05$), 2) effect size (ES), and 3) Educational Testing Services (ETS) Differential Item Functioning (DIF) classification criteria as follows:

- **AA** =negligible DIF
- **BB+** =moderate DIF favoring the focal group (indicating the item appears more uniformly and reliably scored for the severity level vs. the United States)
- **BB-** =moderate DIF favoring the reference group (indicating the item appears more uniformly and reliably scored for the severity level vs. the comparison region)
- **CC+** =large DIF favoring the focal group (indicating the item appears more uniformly scored for the severity level vs. the United States)
- **CC-** =large DIF favoring the reference group (indicating the item appears more uniformly and reliably scored for the severity level vs. the comparison region).



| Sample demographic and clinical characteristics of study population | |
|---|---------------|
| TOTAL NUMBER OF SUBJECTS | 6,889 |
| Male (%) | 4493 (65.22%) |
| Female (%) | 2396 (34.78%) |
| AGE | |
| Mean | 40.12 years |
| SD | 12.35 years |
| AGE AT ONSET | |
| Mean | 25.05 years |
| SD | 8.56 years |
| PANSS TOTAL SCORE | |
| Mean | 83.11 |
| SD | 19.09 |
| PANSS POSITIVE SYMPTOM SUBSCALE SCORE | |
| Mean | 19.49 |
| SD | 6.70 |
| PANSS NEGATIVE SYMPTOM SUBSCALE SCORE | 7-44 |
| Mean | 22.70 |
| SD | 6.93 |
| Range (min-max) | 7-48 |
| PANSS NEGATIVE SYMPTOM FACTOR SCORE | |
| Mean | 21.45 |
| SD | 6.98 |
| Range (min-max) | 7-48 |

- There were 16 cases of large DIF (CC) identified by ○ and 21 cases of moderate DIF (BB) for expressive deficit items (out of 60 total item-by-region comparisons), as compared with four cases of large DIF and 10 cases of moderate DIF for experiential deficit.
- The following regions showed moderate-to-large DIF for all items of the expressive deficit factor: Austria-Germany, Nordic, France, and Poland. Similarly, Austria-Germany, Brazil, and South Africa showed large DIF (CC) for three items of the expressive factor. France and Spain showed large DIF (CC) for N3 Poor Rapport and N6 Lack of Spontaneity and Flow of Conversation as compared with the United States.
- Of all the items of the NSF, N3 Poor Rapport showed the most moderate and large DIF (n=13; 86.67%) across countries, with seven countries reporting large DIF.
- Out of all the factors of the NSF, item G16 Active Social Avoidance reported negligible DIF for 14 of the 15 countries investigated (93.33%). Large DIF was observed for N2 Emotional Withdrawal and N4 Passive Apathetic Social Withdrawal for Brazil and India. Brazil demonstrated the largest DIF classifications (CC) across all countries (i.e., five of the seven NSF items).

RESULTS

| Differential Item Functioning of PANSS expressive and experiential deficits with the United States as the reference geographical region | | | | | | | |
|---|---------------------------|-----------------|------------------------|----------------------|-----------------------------|--|-----------------------------|
| GEOGRAPHICAL REGION | PANSS EXPRESSIVE DEFICITS | | | | PANSS EXPERIENTIAL DEFICITS | | |
| | N1 BLUNTED AFFECT | N3 POOR RAPPORT | N6 LACK OF SPONTANEITY | G7 MOTOR RETARDATION | N2 EMOTIONAL WITHDRAWAL | N4 PASSIVE/APATHETIC SOCIAL WITHDRAWAL | G16 ACTIVE SOCIAL AVOIDANCE |
| South America-Mexico | | | | | | | |
| p | 0.44 | <0.001 | <0.001 | 0.15 | 0.33 | 0.07 | 0.03 |
| ES | 0.03 | 0.54 | 0.35 | 0.09 | 0.04 | 0.13 | 0.16 |
| ETS Class | AA | BB+ | BB+ | AA | AA | AA | AA |
| Austria-Germany | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.01 |
| ES | 0.51 | 0.8 | 0.78 | 0.68 | 0.41 | 0.34 | 0.17 |
| ETS Class | BB+ | CC+ | CC+ | CC+ | BB+ | BB+ | AA |
| Belgium-Netherlands | | | | | | | |
| p | <0.001 | <0.001 | 0.03 | <0.001 | 0.04 | 0.28 | 0.25 |
| ES | 0.23 | 0.48 | 0.2 | 0.31 | 0.13 | 0.07 | -0.09 |
| ETS Class | AA | BB+ | AA | BB+ | AA | AA | AA |
| Brazil | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.01 |
| ES | 0.78 | 0.99 | 0.68 | -0.29 | 0.75 | 0.66 | -0.25 |
| ETS Class | CC+ | CC+ | CC+ | AA | CC+ | CC+ | AA |
| Canada | | | | | | | |
| p | <0.001 | <0.001 | 0.02 | 0.27 | <0.001 | <0.001 | 0.02 |
| ES | 0.2 | 0.17 | 0.14 | -0.06 | 0.24 | 0.31 | 0.13 |
| ETS Class | AA | AA | AA | AA | AA | BB+ | AA |
| Nordic | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.37 |
| ES | 0.31 | 0.54 | 0.38 | 0.32 | 0.26 | 0.27 | -0.04 |
| ETS Class | BB+ | BB+ | BB+ | BB+ | AA | AA | AA |
| France | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.14 |
| ES | 0.44 | 0.91 | 0.67 | 0.53 | 0.42 | 0.53 | 0.1 |
| ETS Class | BB+ | CC+ | CC+ | BB+ | BB+ | BB+ | AA |
| Great Britain | | | | | | | |
| p | 0.89 | <0.001 | 0.02 | 0.42 | 0.04 | <0.001 | 0.21 |
| ES | -0.02 | 0.33 | 0.23 | 0.07 | 0.17 | 0.27 | 0.13 |
| ETS Class | AA | BB+ | AA | AA | AA | AA | AA |
| India | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.55 |
| ES | -0.87 | -0.09 | -0.57 | -0.47 | -0.75 | -0.7 | 0.06 |
| ETS Class | CC- | AA | BB- | BB- | CC- | CC- | AA |
| Italy | | | | | | | |
| p | 0.27 | <0.001 | <0.001 | 0.01 | 0.07 | <0.001 | <0.001 |
| ES | 0.13 | 1 | 0.45 | 0.29 | 0.17 | 0.59 | 0.36 |
| ETS Class | AA | CC+ | BB+ | AA | AA | BB+ | BB+ |
| Poland | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.01 |
| ES | 0.47 | 0.49 | 0.41 | 0.41 | 0.43 | 0.29 | 0.18 |
| ETS Class | BB+ | BB+ | BB+ | BB+ | BB+ | AA | AA |
| Eastern Europe | | | | | | | |
| p | 0.26 | <0.001 | 0.02 | 0.01 | 0.64 | 0.86 | 0.11 |
| ES | 0.08 | 0.34 | 0.17 | 0.16 | 0.03 | 0.001 | -0.09 |
| ETS Class | AA | BB+ | AA | AA | AA | AA | AA |
| Russia | | | | | | | |
| p | <0.001 | <0.001 | 0.03 | 0.54 | <0.001 | 0.01 | 0.06 |
| ES | 0.41 | 0.63 | 0.24 | -0.05 | 0.27 | 0.23 | -0.19 |
| ETS Class | BB+ | CC+ | AA | AA | AA | AA | AA |
| South Africa | | | | | | | |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.16 |
| ES | 0.79 | 0.76 | 0.63 | 0.23 | 0.31 | 0.38 | -0.07 |
| ETS Class | CC+ | CC+ | CC+ | AA | BB+ | BB+ | AA |
| Spain | | | | | | | |
| p | 0.01 | <0.001 | 0.01 | 0.18 | 0.06 | 0.41 | 0.31 |
| ES | 0.27 | 0.62 | 0.32 | 0.13 | 0.18 | 0.08 | -0.11 |
| ETS Class | AA | CC+ | CC+ | AA | AA | AA | AA |
| Differential Item Functioning (DIF) | | | | | | | |
| Number of large DIF | 3 | 7 | 5 | 1 | 2 | 2 | 0 |
| Number of moderate DIF | 5 | 6 | 5 | 5 | 4 | 5 | 1 |
| Number of negligible DIF | 7 | 2 | 5 | 9 | 9 | 8 | 14 |

PANSS—Positive and Negative Syndrome Scale; ES—effect size; ETS—Education Testing Services; AA—negligible DIF; BB+ =moderate DIF favoring the focal group; BB- =moderate DIF favoring the reference group; CC+ =large DIF favoring the focal group; CC- =large DIF favoring the reference group

CONCLUSIONS

- Despite the multiple psychometric analyses of the PANSS over the past 30 years, this study is the first to assess performance on the PANSS expressive and experiential deficit factors across varying levels of symptom severity and across multiple (i.e., 15) geographical regions.
- The expressive and experiential items of the PANSS NSF show good model fit and distinct deficits in these two domains, indicating that the PANSS expressive deficit and experiential deficit factors can be reliably used as distinct efficacy endpoints to further characterize negative symptoms.
- Negative symptom items show increased variability in scores across raters. Specifically, we showed DIF across multiple countries for most items of the PANSS expressive deficit.
- Training for negative symptoms in global trials has likely been insufficient in that it has not addressed important cultural differences; future training needs to address the items showing large DIF as it is conducted across specific countries and cultures

DISCLOSURES AND CONTACT INFORMATION

A Khan is a full-time employee of NeuroCog Trials, Durham, NC, USA, and has received support from National Institute of Mental Health, Janssen, Celgene, Teva Pharmaceuticals, and Stanley Medical Research Foundation. AS Atkins is a full-time employee of NeuroCog Trials, Durham, NC, USA, and has received support from National Institute of Mental Health. L Liharska and D Ulshen are employees of NeuroCog Trials. L Harper Mozley, T Voss and K Budd McMahon are employees of Merck & Co, Inc., Kenilworth, NJ, USA. RSE Keefe currently or in the past 3 years has received investigator-initiated research funding support from the Department of Veteran's Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. He currently or in the past 3 years has received honoraria, served as a consultant, or advisory board member for AbbVie, Akebia, Amgen, Asubio, AviNeuro/ChemRx, BiolineRx, Biogen Idec, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/FORUM, GW Pharmaceuticals, Janssen, Lundbeck, Merck, Minerva Neurosciences, Inc., Mitsubishi, Novartis, NY State Office of Mental Health, Otsuka, Pfizer, Reviva, Roche, Sanofi/Aventis, Shire, Sunovion, Takeda, Targacept, and the University of Texas South West Medical Center. Dr. Keefe receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding) and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). He is also a shareholder in NeuroCog Trials and Sengenix. Dr. Harvey has served as a consultant to AbbVie, Allergan, Akili, Boehringer Ingelheim, Forum Pharmaceuticals, Genentech, Lundbeck Pharmaceuticals, Otsuka Digital Health, Roche Pharma, Sanofi, Sunovion, and Takeda Pharmaceutical for the past 3 years.

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