Supplementary Material

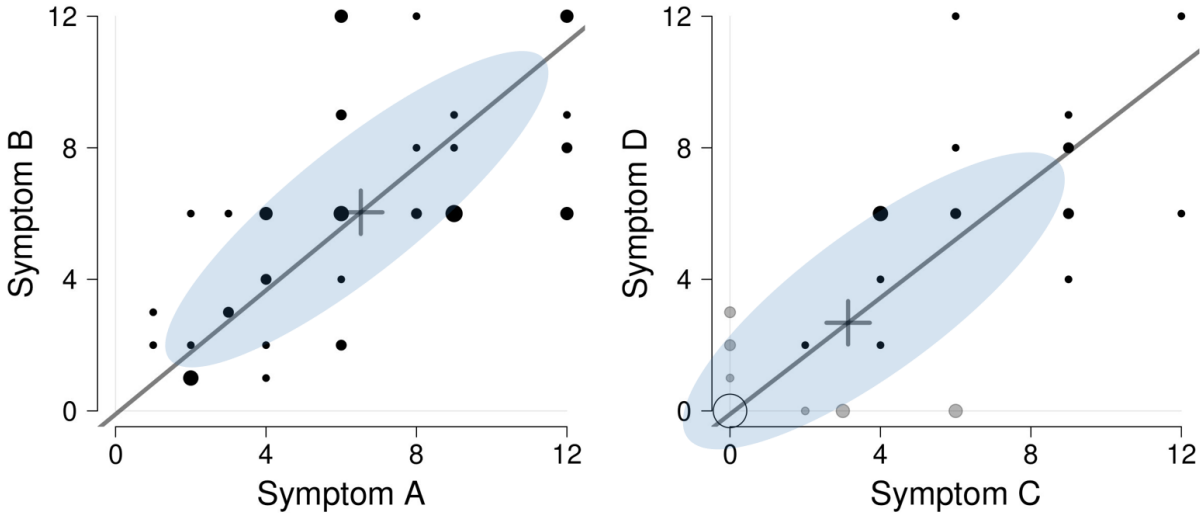
Clusterization of Behavioral and Psychological Symptoms of Dementia as Assessed by Neuropsychiatric Inventory: A Case Against the Use of Principal Component Analysis

Supplementary Material 1: Principal Component Analysis

Left panel of Supplementary Figure 1 illustrates the general idea behind the principal component analysis (PCA) using a scenario where Symptom "A" is clearly associated with Symptom "B". Each circle on the plot represents one or more hypothetical subjects in whom these two symptoms are present with certain scores. Size of the circles is proportional to the number of subjects (observations) with a certain combination of symptom scores. The circles have elliptically symmetric distribution on a bivariate surface with the centroid marked by a cross.

PCA is a method that finds unique directions (principal components) of maximal total variances of multivariate distributions. The first principal component is depicted in Supplementary Figure 1 by the line that comes across the observations. This principal component can be considered as a latent (unobserved) factor that loads information on Symptom "A" and Symptom "B". In such an example of a clear association between two symptoms, most information about the two symptoms can be described just by the first principal component. The second principal component (not shown) would go perpendicular (orthogonally) to the first principal component. In case of multivariate distribution all principal components are orthogonal and thus uncorrelated to each other.

So called "loadings" are Pearson's correlations between a principal component and each symptom. Symptoms with high loadings have strong correlations with the component and with each other. The maximal number of possible principal components is equal to the number of variables in the analysis. For example, for 10 NPI symptoms, there may be derived up to 10 principal components. However, in the presence of associations between symptoms, less than 10 principal components are needed to preserve the majority of information in the dataset. The Guttman-Kaiser rule helps to identify reasonable number of principal components. Varimax and promax rotations are the techniques that help simplify the structure of the loadings.



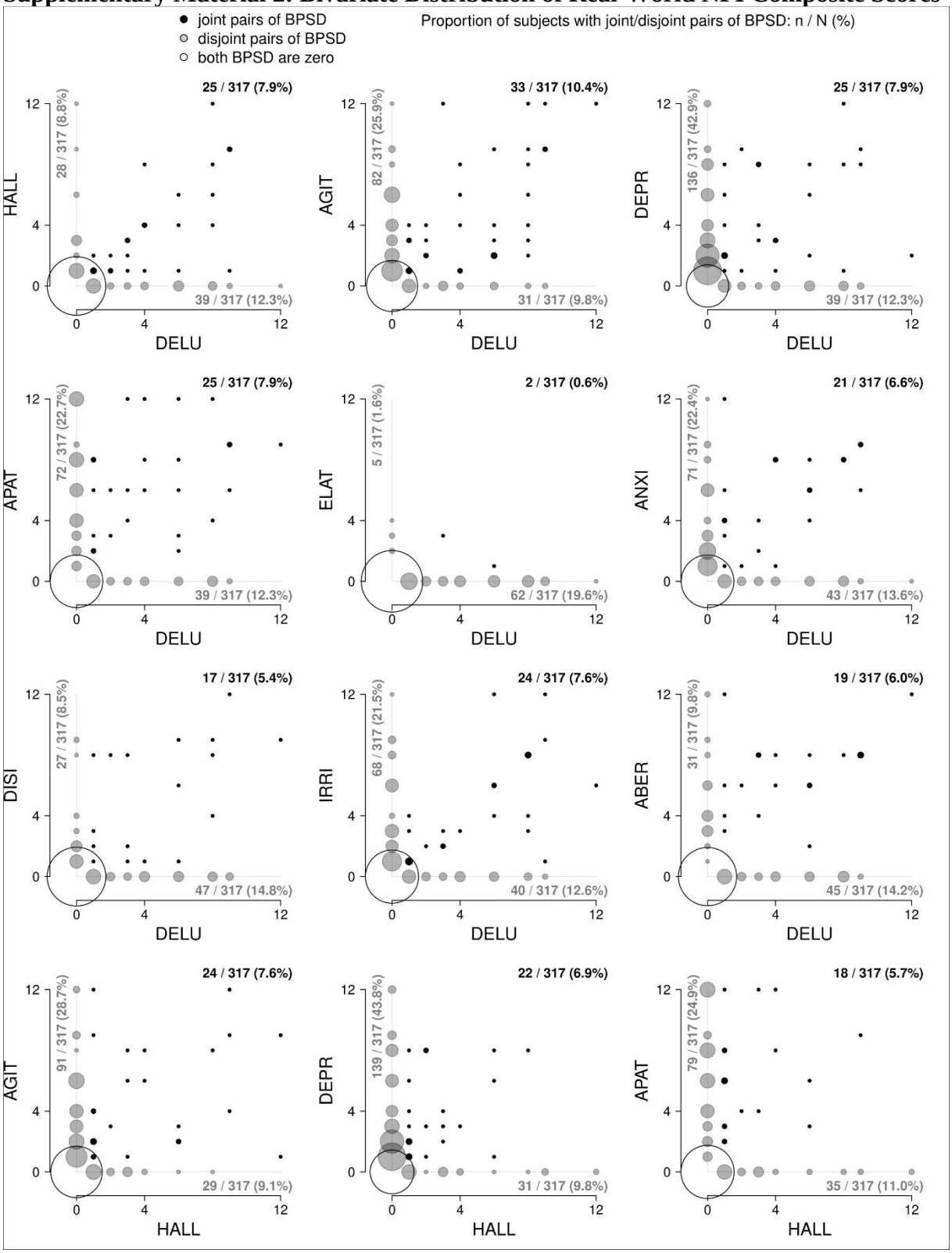
Supplementary Figure 1. Principal component analysis (PCA, left panel) and zero-inflated PCA (right panel) of symptom product scores.
Black circles are joint symptoms (both symptoms have a product score greater than zero), grey circles are disjoint symptoms (one of the symptoms has a product score of zero), empty circle – both symptoms have a product score of zero. Semi-transparent ellipses outline distributions. Size of the circles is proportional to the number of such observations with a given combination of symptom scores. Black line across each plot is the direction of the first principal component. Plus sign in each panel is the distribution centroid (bivariate mean). Please see the main article for the definition of product scores.

Principal component analysis is usually applied to correlation matrix with the Guttman-Kaiser rule (eigenvalues greater than 1) to retrieve the components. Varimax rotation is applied then to the loadings and a loading threshold of about 0.30 is used to retrieve NPI symptoms loaded by each component.

While we refer the readers to Hellton et al. (2021) for detailed explanation of the PCA and ZI PCA [1], zero-inflated distribution is illustrated in the right panel of Supplementary Figure 1. Observations with zero scores are marked by empty or grey circles. This distribution is skewed away from zero and still lies along the first principal component. Intuitive explanation of such distribution is clear: there are healthy subjects with no symptoms (the empty circle), subjects with just one mild symptom (the grey circles), and more severe cases with both clearly associated symptoms (the black circles).

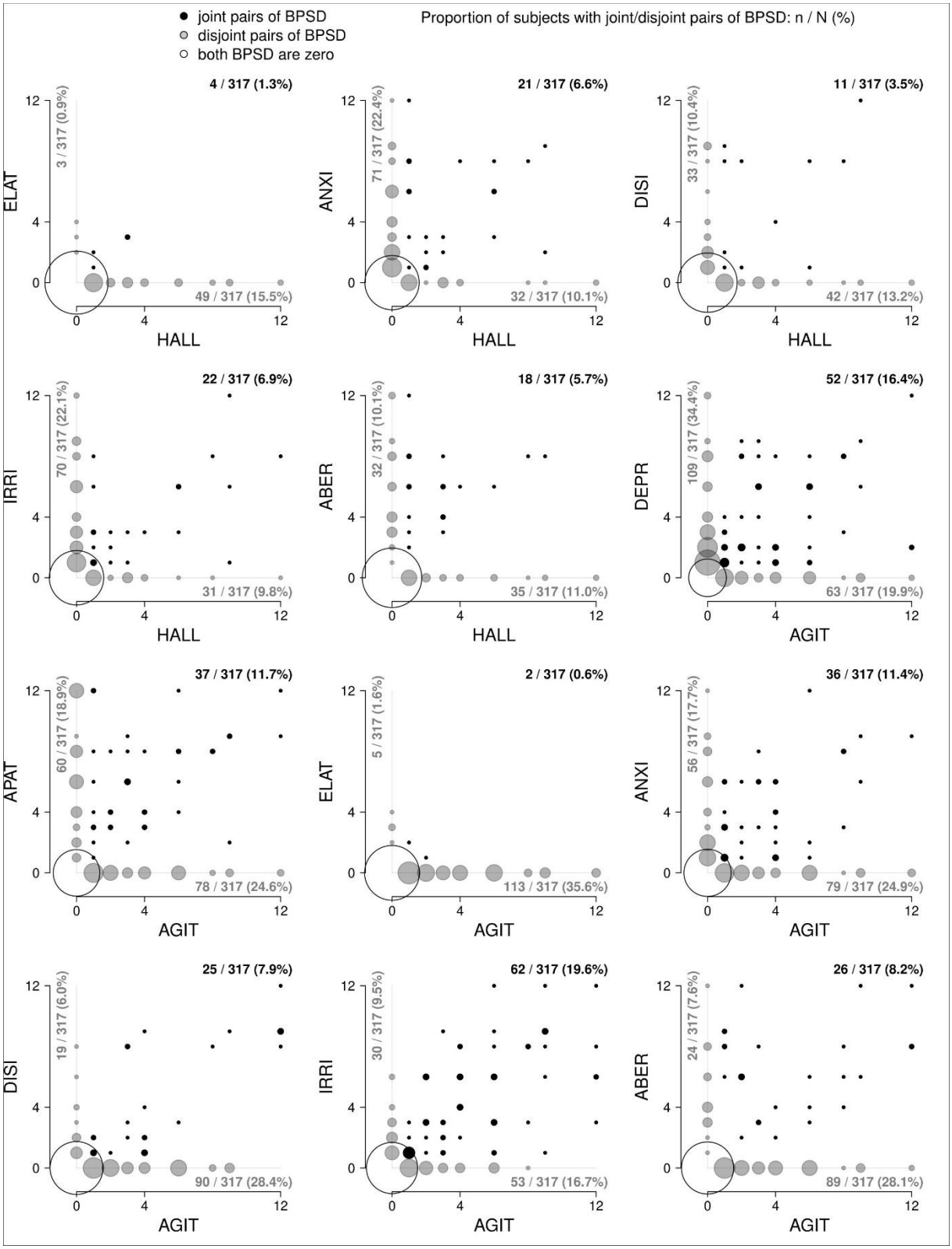
Further, Hellton et al. suggested to use promax rotation of components instead of varimax rotation (the number of components was still defined by the Guttman-Kaiser rule) and a 0.40 threshold for loadings.

Supplementary Material 2: Bivariate Distribution of Real-World NPI Composite Scores

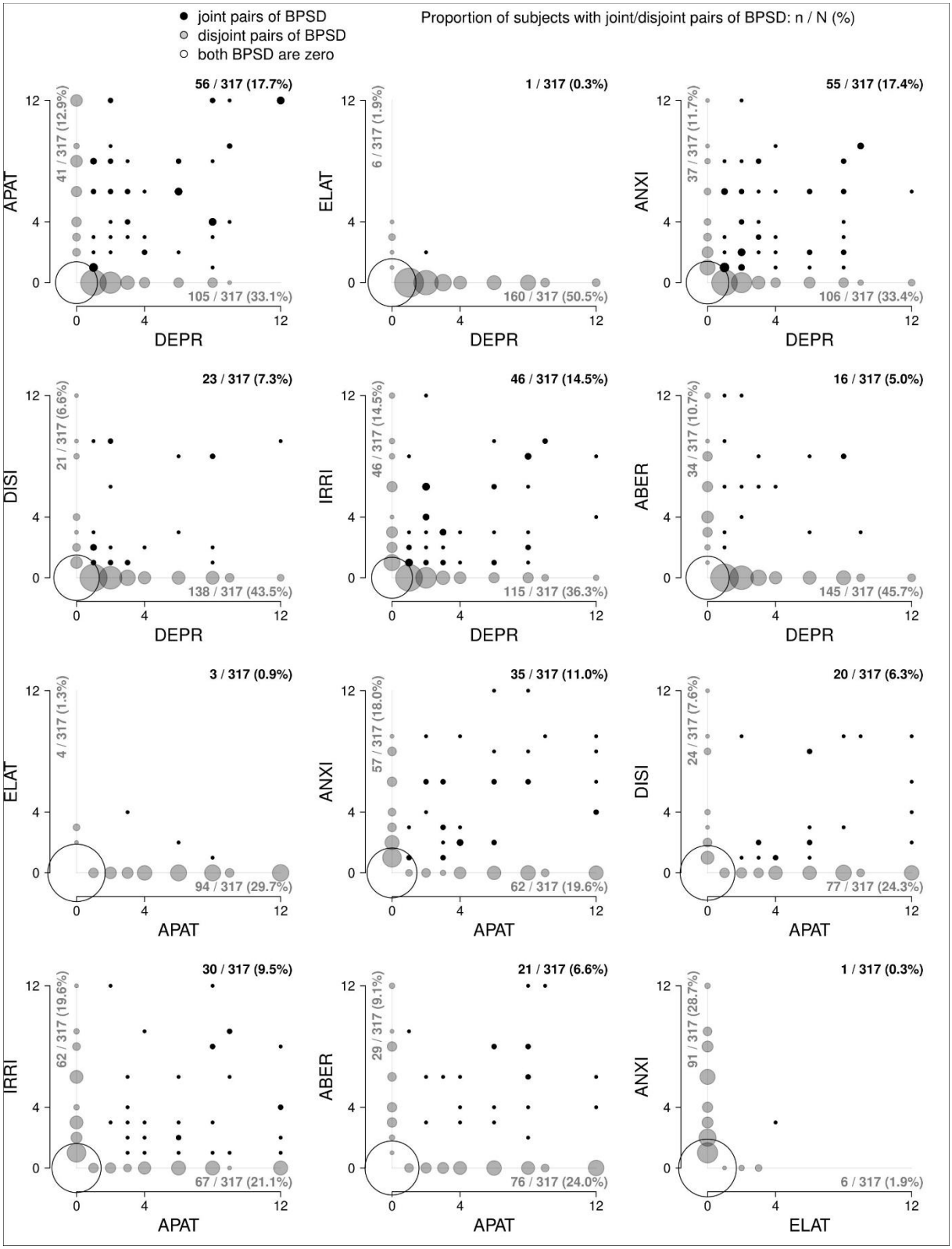


Supplementary Figure 2. Bivariate distributions of real NPI scores in ADAMS Wave A

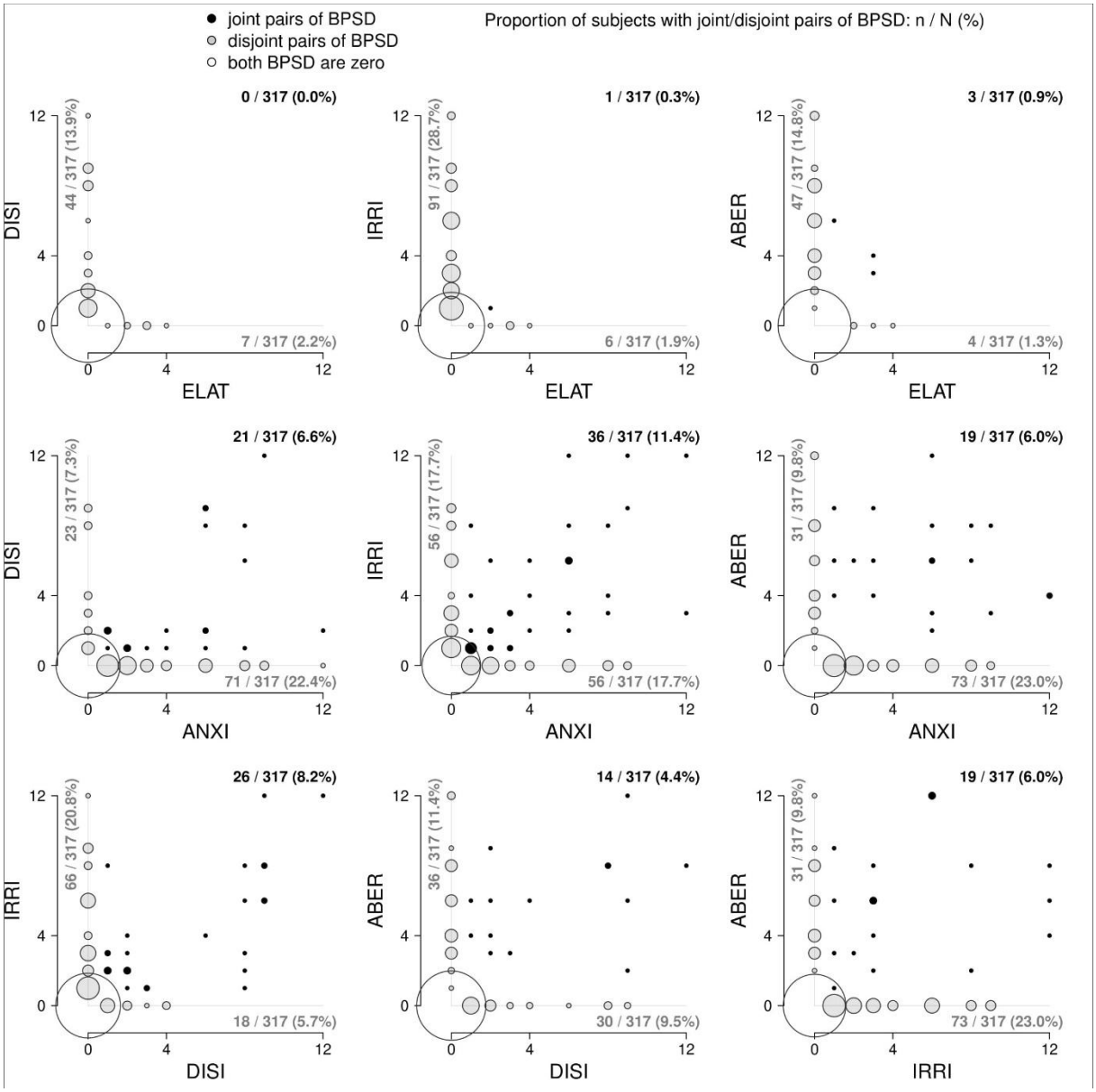
A total of 317 subjects that had at least 1 BPSD (NPI composite score > 0) were used to produce these plots. The circle size is proportional to the number of subjects with the corresponding combination of product scores for the indicated pairs of symptoms. Subjects with both BPSD present (joint pairs of BPSD) are depicted with black circles; proportions of these subjects are denoted in the upper right corner of each plot. Subjects that had one of the two symptoms (disjoint pairs of BPSD) are depicted with grey circles, their proportions are denoted next to X and Y axes. Empty circle – both symptoms are zero.



Supplementary Figure 2 (continued)



Supplementary Figure 2 (continued)



Supplementary Figure 2 (continued)

Supplementary Material 3: Publications that Used PCA for Analysis of Behavioral and Psychological Symptoms of Dementia

At the time of writing this manuscript (27 July 2023), a search in PubMed using a combination of the terms “"neuropsychiatric inventory" AND ("principal component analysis" OR "factor analysis")” provided a list of 122 publications. The term “factor analysis” was included as the majority of publications labeled principal component analysis as “factor analysis”. Forty-five full-length publications met the criteria and were initially included in the analysis. Three additional publications were identified later in the publications’ reference lists.

Reference number	First author (y)	PMID	NPI version	NPI outcome	Exclusion of subjects with all zero NPI scores	Normalization of NPI items	Method	Rotation of loadings	Factor extraction criteria	Threshold for loadings
[2]	Aarsland et al. (1999)	10486397	NPI 10	UN*	UN*	UN*	PCA	UN*	UN*	UN*
[3]	Frisoni et al. (1999)	10026387	NPI 10	Product scores	Yes*	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.30
[4]	Aalten et al. (2003)	12566599	NPI 12	Product scores	Yes*	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.45
[5]	Mirakhur et al. (2004)	15481075	NPI-12	Product scores	Yes*	Yes	PCA	Varimax, Equamax and Quartimax	Eigenvalues ≥ 1.00	≥ 0.50
[6]	Spalletta et al. (2004)	15311344	NPI 10	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 0.80	≥ 0.45
[7]	Gauthier et al. (2005)	15852444	NPI-12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.45
[8]	Borroni et al. (2006)	16257094	NPI 12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.45
[9]	Cummings et al. (2006)	16816014	NPI-12	Product scores	No	Yes	PCA	Promax	Eigenvalues ≥ 1.00	UN *
[10]	Hollingworth et al. (2006)	16970641	NPI 12	Product scores	No	Yes	PCA on polychoric correlations	Oblique *	Eigenvalues ≥ 1.00, scree plot, interpretability of factors	≥ 0.40
[11]	Matsui et al. (2006)	16401890	NPI 10	Product scores	No	UN *	UN *	Varimax	UN *	*
[12]	Aalten et al. (2007)	17986816	NPI 12	Product scores	Yes	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40

Reference number	First author (y)	PMID	NPI version	NPI outcome	Exclusion of subjects with all zero NPI scores	Normalization of NPI items	Method	Rotation of loadings	Factor extraction criteria	Threshold for loadings
[13]	Archer et al. (2007)	17322133	NPI 10	Product scores	No	Yes	PCA	Direct oblimin	Eigenvalues ≥ 1.00	≥ 0.40
[14]	Colombo et al. (2007)	17317443	NPI-12	Product scores	No	Yes *	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40 *
[15]	Petrovic et al. (2007)	18351187	NPI-12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[16]	Starr et al. (2007)	17890863	NPI 10	Product scores	No	*	PCA	Varimax	UN *	Not used
[17]	Aalten et al. (2008)	18025783	NPI 12	Product scores	Yes	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[18]	Dechamps et al. (2008)	18484678	NPI-NH	Product scores	No	UN *	PCA	UN *	UN *	≥ 0.40
[19]	Spalletta et al. (2010)	20808086	NPI 10	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 0.80	≥ 0.50
[20]	Vilalta-Franch et al. (2010)	20220583	NPI 10	Product scores	Yes*	Yes	PCA	Promax	Eigenvalues ≥ 1.00	≥ 0.45
[21]	Cravello et al. (2011)	20678302	NPI-12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.50
[22]	Bettney et al. (2012)	22250004	NPI 12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[23]	Chen et al. (2012)	21617520	NPI 12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00, scree plot	≥ 0.45*
[24]	Lee et al. (2012)	22835209	NPI 12	Product scores	No	UN *	PCA	Varimax	UN *	≥ 0.40
[25]	Nomura et al. (2012)	22994619	NPI 8 #	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.30
[26]	Selbæk & Engedal (2012)	21682940	NPI-NH	Product scores	No	Yes	PCA	Direct oblimin	Eigenvalues ≥ 1.00	≥ 0.40
[27]	Khoo et al. (2013)	24230964	NPI-12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[28]	Poletti et al. (2013)	23154430	NPI-12	Product	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	UN*

Reference number	First author (y)	PMID	NPI version	NPI outcome	Exclusion of subjects with all zero NPI scores	Normalization of NPI items	Method	Rotation of loadings	Factor extraction criteria	Threshold for loadings
				scores						
[29]	Truzzi et al. (2013)	23113901	NPI 10	Product scores	No	*	PCA	Varimax	UN *	≥ 0.40
[30]	Apostolova et al. (2014)	24481207	NPI 10	Product scores	No	UN*	PCA	Varimax	UN*	≥ 0.25
[31]	Ho et al. (2016)	27572478	NPI-12	Product scores	No	Yes	PCA	Oblique *	Eigenvalues ≥ 1.00	≥ 0.40
[32]	Kazui et al. (2016)	27536962	NPI 12	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.30
[33]	Nagata et al. (2016)	26836181	NPI 12	Product scores	No	Yes	PCA	Promax	Eigenvalues ≥ 1.00	≥ 0.50
[34]	Reuther et al. (2016)	26739512	NPI-NH	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00, scree plot	≥ 0.40
[35]	Yesavage et al. (2016)	27115509	NPI 12	Product scores	No	Yes	PCA	*	Eigenvalues ≥ 1.00	≥ 0.40
[36]	Siafarikas et al. (2017)	28927477	NPI-Q	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[37]	Vaingankar et al. (2017)	28416031	NPI-12	Product scores	No	Yes	PCA	Promax	Eigenvalues ≥ 1.00	≥ 0.45
[38]	Zhong et al. (2017)	28538242	NPI 10	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[39]	Chen et al. (2018)	29409164	NPI-NH	Product scores	No	Yes	PCA	Varimax	Eigenvalues ≥ 1.00, scree plot	≥ 0.40
[40]	Connors et al. (2018)	29548721	NPI 10	Product scores	No	Yes	PCA	Direct oblimin	Eigenvalues ≥ 1.00, scree plot, interpretability of factors	UN *
[41]	Lundqvist et al. (2020)	32367679	NPI-ID	Product scores	No	Yes	PCA	Promax	Eigenvalues ≥ 1.00	≥ 0.30
[42]	Regier et al. (2020)	32363605	NPI-C	Product scores	No	Yes	PCA	Direct oblimin	Eigenvalues ≥ 1.00, scree plot, parallel analysis, the optimal coordinate method, the comparative data technique, factor interpretability	≥ 0.30

Reference number	First author (y)	PMID	NPI version	NPI outcome	Exclusion of subjects with all zero NPI scores	Normalization of NPI items	Method	Rotation of loadings	Factor extraction criteria	Threshold for loadings
[1]	Hellton et al. (2020)	32329370	NPI 12	Sum scores	Yes	Yes	Zero-inflated bivariate Poisson PCA	Promax	Eigenvalues ≥ 1.00	≥ 0.40
[43]	Fishman et al. (2004)	15377743	NPI *	Product scores	UN*	UN*	PCA (?) *	Varimax	UN*	≥ 0.50
[44]	Marvardi et al. (2005)	15847122	NPI *	Product scores	UN*	UN*	PCA (?) *	UN*	UN*	UN*
[45]	Zuidema et al. (2007)	17641527	NPI *	Product scores	No	Yes	PCA (?) *	Varimax	Eigenvalues ≥ 1.00	≥ 0.40
[46]	Garre-Olmo et al. (2010)	20930289	NPI *	Product scores	No	Yes	PCA (?) *	Promax	Eigenvalues ≥ 1.00	≥ 0.30
[47]	Munro et al. (2015)	25854929	NPI *	Product scores	UN*	UN*	PCA (?) *	UN*	UN*	UN*
[48]	Wada-Isoe et al. (2020)	32587948	NPI *	Product scores	No	UN*	PCA (?) *	Promax	UN*	UN*

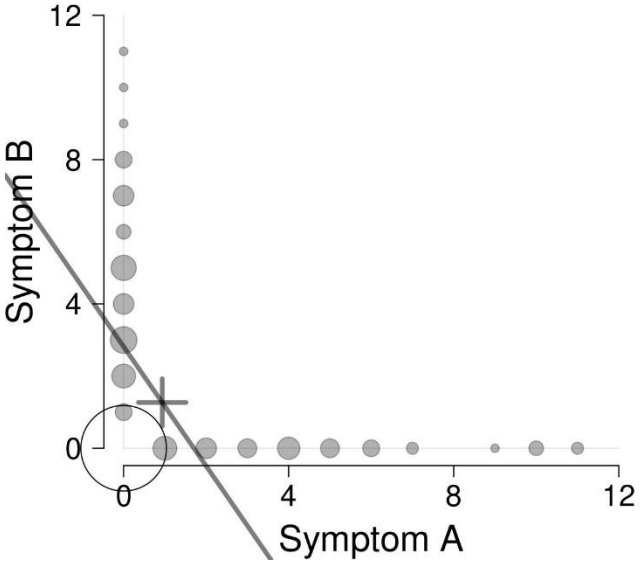
NPI, Neuropsychiatric Inventory; NH, Nursing Home version; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPI-ID, Neuropsychiatric Inventory Intellectual Disability; NPI-C, Neuropsychiatric Inventory Clinician rating scale; PCA, principal component analysis. Product scores = frequency × severity. * Not clearly stated by the authors. # The authors analyzed 8 types of delusions. UN, unknown

Supplementary Material 4: Illustration of the Principal Component Analysis of an Overlapping Distribution Mixture

Supplementary Figure 3 illustrates inability of the principal component analysis (PCA) to adequately fit an overlapping distribution mixture. Axis vectors A and B on the figure span the two-dimensional analysis vector space AB. Axis A and axis B represent two orthogonal one-dimensional subspaces A and B that intersect at zero point. We can say that symptom A scores and symptom B scores overlap by sharing zero scores.

PCA's algorithm minimizes squared distance from the first principal component to each data point. In the presence of overlapping orthogonal subspaces the only solution would be to lay the first principal component outside of the data subspaces. As shown in Supplementary Figure 3, the first principal component lies within the analysis space AB but outside of the data subspaces A and B.

More generally, overlapping NPI patterns are orthogonal 1-2-3-…-dimensional subspaces of NPI symptoms that intersect in a 10-dimensional NPI vector space. For example, symptom associations {"C", "D"} and {"C", "E"} span two orthogonal planes (subspaces) that intersect each other along axis C. In other words, symptom associations {"C", "D"} and {"C", "E"} overlap by sharing symptom C. Under such circumstances, principal components always lay outside of the subspaces, that is, they do not fit the data. Further varimax or promax rotation may partially improve the fit, but not always as it is shown in the main simulation described in the article.



Supplementary Figure 3. The principal component analysis of symptom product scores
Grey circles are disjoint symptoms (one of the symptoms has a product score of zero), empty circle – both symptoms have a product score of zero. Size of the circles is proportional to the number of such observations with a given combination of symptom scores. Black line is the first principal component. Plus sign is the distribution centroid (bivariate mean). See text for explanation.

Supplementary Material 5: Additional Simulations

In this supplement, we show the results of additional simulations with random patterns.

We made a list of all 1,023 possible patterns (i.e., all combinations of 10 symptoms, excluding the all-noise pattern). Each of the scenarios described below was simulated in 1,000 iterations. Each iteration started with a random sampling of a set of 4 (scenarios 1 and 2) or 8 (scenario 3) patterns from this list. To preserve a realistic balance of mono-symptoms, double, triple and more complex symptom associations, each sample of 4 patterns in the first and second scenarios included 2 random mono-symptoms, 1 random association of 2 symptoms, and 1 random association of ≥3 symptoms; each sample of 8 patterns in the third scenario included 4 random mono-symptoms, 2 random associations of 2 symptoms, and 2 random association of ≥3 symptoms. Each symptom association was simulated with 30 subjects, each mono-symptom was simulated with 90 subjects as mono-symptoms are much more frequent in real data in ADAMS.

Thus, at each iteration, datasets with 240 subjects (90*2+30*2) were simulated in scenarios 1 and 2, while there were 480 subjects (90*4+30*4) in scenario 3. Each scenario was iterated 1,000 times, as was already mentioned above. For more details, see Materials and Methods in the article.

Scenarios 2 and 3 were simulated with the aim to generate overlapping patterns. However, for scenario 1, we added one restriction: random patterns drawn at each iteration step could not overlap. In order to comply with this restriction, the first step at each iteration was to draw two random mono-symptoms, followed by a random association of two symptoms that did not overlap with the previously drawn mono-symptoms, then a random association of three or more symptoms that did not overlap with any of the previously drawn patterns.

The results of the principal component analysis (PCA) and zero inflated (ZI) PCA are shown in the table below.

Scenario 1 4 random non-overlapping patterns, 1000 iterations				
Type of patterns	True/ False	Mean number of detected patterns at one iteration (% of correct patterns, if applicable)		
		Correct numbers	PCA	ZI PCA
Mono-symptoms	True	2.00 (100%)	0.49 (24.0%)	0.25 (13.0%)
	False	0.00	0.36	0.07
Symptom associations	True	2.00 (100%)	1.96 (98.0%)	2.00 (100.0%)
	False	0.00	1.09	1.57

Scenario 2 4 random overlapping patterns, 1000 iterations				
Type of patterns	True/ False	Mean number of detected patterns at one iteration (% of correct patterns, if applicable)		
		Correct numbers	PCA	ZI PCA
Mono-symptoms	True	2.00 (100%)	0.17 (8.0%)	0.38 (19.0%)
	False	0.00	0.52	0.31
Symptom associations	True	2.00 (100%)	1.49 (74.0%)	0.95 (47.0%)
	False	0.00	1.49	2.30
Scenario 3 8 random overlapping patterns, 1000 iterations				
Type of patterns	True/ False	Mean number of detected patterns at one iteration (% of correct patterns, if applicable)		
		Correct numbers	PCA	ZI PCA
Mono-symptoms	True	4.00 (100%)	0.28 (7.0%)	0.86 (21.0%)
	False	0.00	0.23	0.24
Symptom associations	True	4.00 (100%)	1.81 (45.0%)	0.94 (23.0%)
	False	0.00	1.22	2.21

PCA and ZI PCA detected all symptom associations (98.0% and 100.0% accordingly) in the first scenario. This result is explained by the fact that the distribution mixtures in scenario 1 did not overlap.

However, in the second scenario with overlapping distribution mixtures efficiency of PCA and ZI PCA dropped to 74.0% and 47.0%, respectively. As explained in the main text, ordinary PCA is not well suited to be used as an analytical tool for such distribution mixtures.

Finally, when the number of patterns was increased to 8 (scenario 3), efficiency of PCA and ZI PCA dropped further to 45.0% and 23.0%, respectively.

Both PCA and ZI PCA were very inefficient in detecting mono-symptoms: detection rates were as low as 24.0% and 13.0% accordingly even for the first scenario of non-overlapping patterns.

Both PCA and ZI PCA had a high rate of false detections even for the first scenario: for every two correct detections of symptom associations there was one incorrect detection for PCA and 1.5 incorrect detection for ZI PCA.

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