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Consistency of Neuropsychiatric Syndromes across Dementias: Results from the European Alzheimer Disease Consortium

Part II

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Key Words

Neuropsychiatric syndromes · Neuropsychiatric analysis · Dementia · Subsyndromes · European Alzheimer's Disease Consortium

Abstract

Background/Aims: The aim of this study was to determine the consistency of neuropsychiatric subsyndromes of the Neuropsychiatric Inventory across several clinical and demographic subgroups (e.g. dementia subtypes, dementia severity, medication use, age and gender) in a large sample of outpatients with dementia. ***Methods:*** Cross-sectional data of 2,808 patients with dementia from 12 centres from the European Alzheimer's Disease Consortium were collected. Principal component analysis was used for factor analysis. Subanalyses were performed for dementia subtypes, dementia severity, medication use, age and gender. ***Results:*** The results showed the relatively consistent presence of the 4 neuropsychiatric subsyndromes 'hyperactivity', 'psychosis', 'affective symptoms' and 'apathy' across the subanalyses. The factor structure was not dependent on dementia subtypes, age and gender but was dependent on dementia severity and cholinesterase use. The factors hyperactivity and affective symptoms were present in all subanalyses, but the presence of the factors apathy and psychosis was dependent on use of cholinesterase inhibitors and dementia severity, respectively. ***Conclusion:*** The present study provided evidence of the relative consistency of neuropsychiatric subsyndromes across dementia subtypes, age and gender,

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thereby stressing the importance of thinking about neuropsychiatric subsyndromes instead of separate symptoms. However, the subsyndromes apathy and psychosis were dependent on use of cholinesterase inhibitors and dementia severity.

Introduction

Recent studies have provided increasing evidence of the existence of neuropsychiatric subsyndromes in dementia [1–9]. Most of these studies included only patients with Alzheimer's disease (AD) [1, 3–6, 9, 10], whereas others included patients with various dementia subtypes [2, 8]. Recently, the Behavioural Subgroup of the European Alzheimer's Disease Consortium (EADC) has performed a factor analysis of the Neuropsychiatric Inventory (NPI) in a homogeneous sample of patients with AD [3]. This resulted in a robust conclusion regarding the presence of neuropsychiatric syndromes by analyzing the largest AD population ever studied for this purpose. The study identified 4 separate neuropsychiatric subsyndromes: hyperactivity, psychosis, an affective syndrome and apathy. Nevertheless, it was acknowledged that the study was limited by the inclusion of patients with AD only, which implies that the conclusions could not necessarily be generalized to dementias with other aetiologies.

In addition, besides the influence of different dementia subtypes on the outcome of neuropsychiatric subsyndromes in dementia, other variables such as severity of dementia, gender, age and use of medication may be of influence as well, but these have not been taken into account in most studies. Only Aalten et al. [2] and Hollingworth et al. [1] looked at differences in factor structure between patients with relatively mild versus severe dementia [11], but they both found minor changes. Furthermore, Aalten et al. [2] reported a separate analysis for only patients with AD resulting in a factor structure analogous to that found for the total group of patients with different dementia subtypes. Nevertheless, the studies of Aalten et al. [2] and Hollingworth et al. [1] did not look at differences in factor structure in other dementia subtypes, and differences related to age, gender and medication.

The aim of the present study was to determine the consistency of neuropsychiatric subsyndromes of the NPI across several clinical and demographic subgroups, in a relatively large sample of patients with dementia from several centres from the EADC. It was hypothesized that in line with the previous study of the EADC data [3], including only AD, the 4 separate neuropsychiatric subsyndromes are consistent across different clinical and demographic subgroups within dementia. Subanalyses were performed for dementia subtypes, dementia severity, medication use, age and gender, resulting in separate clinical and demographic subgroups. This article produced by the Behavioural Subgroup of the EADC aims at coming to conclusions about the consistency of neuropsychiatric subsyndromes in patients with dementia across several subgroups, by including the largest number of patients with dementia into this research area until now.

Methods

Patients

Patient data were collected by pooling several retrospective datasets from ongoing and past studies carried out by 12 research centres participating in the Behavioural Subgroup of the EADC, representing 12 European countries (www.alzheimer-europe.org/EADC). In addition, patients were included from the REAL-FR data, based on data from centres in the French national network. The EADC is a consortium of 47 Alzheimer's centres in 13 European countries and is funded by the European Union for the purpose of defining operational standards of excellence for the diagnosis and treatment of patients suffering from cognitive and behavioural disturbances [12]. For the present study only centres were included that could provide a minimal dataset; demographic data including age and gender; clinical diagnosis of dementia as determined by the DSM-IV and ICD-10 criteria, including all different causes of dementia; severity of dementia as assessed by the Mini Mental State Examination (MMSE); and neuropsychiatric symptoms as assessed by the NPI. The combined dataset consisted of 2,808 outpatients with a clinical diagnosis of dementia. All patients had at least 1 clinically relevant neuropsychiatric symptom as defined by the NPI (score >3). Some centres contributed data about a relatively large number of patients. Studies encompassing >300 patients were Toulouse (ICTUS study, 491 patients), the REAL-FR dataset (488 patients) and a study from Perugia, Italy (781 patients). All data were collected in accordance with local research governance. Where appropriate, ethical approval for data collection was obtained by each centre.

Neuropsychiatric Inventory

All studies used the NPI for the assessment of neuropsychiatric symptoms [13], a retrospective (up to 1 month) informant-based rating scale for psychopathology in patients with dementia. The current version [14] evaluates 12 neuropsychiatric symptoms commonly observed in dementia: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. The severity and frequency of each symptom are scored on the basis of structured questions administered to the patient's caregiver. The continuous score for each symptom is obtained by multiplying severity (1–3) by frequency [1–4]. The content validity, concurrent validity, in-

Table 1. Factor analysis of the NPI (total group; n = 2,808)

	Factor 1: hyperactivity	Factor 2: psychosis	Factor 3: affective	Factor 4: apathy
Delusions	0.240	*0.732*	0.092	–0.027
Hallucinations	0.097	*0.817*	0.052	–0.007
Agitation	*0.611*	0.164	0.387	0.042
Depression	–0.023	0.030	*0.726*	0.198
Anxiety	0.051	0.100	*0.748*	–0.026
Euphoria	*0.548*	–0.075	–0.229	0.058
Apathy	0.097	–0.099	0.173	*0.659*
Disinhibition	*0.692*	0.159	–0.005	0.022
Irritability	*0.610*	0.164	0.389	0.047
Aberrant motor behaviour	*0.415*	0.309	–0.050	0.376
Night-time behaviour disturbances	–0.059	*0.499*	0.140	*0.438*
Appetite and eating abnormalities	0.034	0.075	–0.026	*0.721*
Eigenvalues	2.793	1.273	1.127	1.088
Variance, %	23.27	10.61	9.39	9.07

Italics indicate factor loading ≥0.40.

ter-rater reliability and test-retest reliability of the original English NPI have been established [15]. In addition, the validity and reliability of the NPI have also been established across different languages, like the French version [16], Italian version [4] and its Dutch version [17].

In line with previous studies, a score >3 was taken to indicate the presence of 'clinically relevant' symptoms [18–22]. The 12-item NPI was available for 2,573 patients (91.6%) because 2 centres administered the 10-item NPI.

Procedure

All centres participating in the behavioural subgroup of the EADC were asked to gather their NPI data and send them, together with demographic and clinical data, to the co-coordinating centre in Maastricht, The Netherlands. All data were converted into the Statistical Package for Social Sciences (SPSS), version 12, for analysis. Demographic data included age, gender and country. Clinical data included dementia aetiology, use of cholinesterase inhibitors (yes-no) and antipsychotics (yes-no). The MMSE [23] was used as a global measure of cognitive functioning.

Statistical Analysis

Statistical analysis was performed with SPSS, version 12. Principal component analyses were performed on all 12 NPI items to detect neuropsychiatric subsyndromes, using an orthogonal rotational procedure (Varimax). Factors were selected on the basis of eigenvalues >1. Factor loadings ≥0.40 were included [2]. Separate subanalyses were performed to determine the consistence of the neuropsychiatric subsyndromes across different groups based on clinical variables. These subanalyses were performed for gender, use of cholinesterase inhibitors and antipsychotics (yes-no), age, MMSE and aetiology. Global cognitive decline was expressed as mild (MMSE scores >20), moderate (MMSE scores between 20 and 11) and severe (MMSE scores ≤10). Patients were grouped by age as follows: youngest (40–65 years), middle (66–75 years) and oldest (76–99 years).

Results

Characteristics of the Patients

Of the 2,808 included patients, 2,354 (83.8%) met the criteria for dementia of the Alzheimer type. One hundred fifty-two patients (5.4%) had vascular dementia, 134 (4.8%) Lewy body dementia, 53 (1.9%) frontal temporal dementia, 7 Parkinson dementia, 4 primary progressive aphasia, 49 other aetiologies of dementia, and from 55 (2%) of the patients the diagnosis was missing.

A total of 952 men (33.9%) and 1,856 women (66.1%) were included in the study. The mean age was 76.5 ± 7.9 years (range = 40–99). The average MMSE was 17.6 ± 6.1 (range = 0–30), indicating in general the inclusion of patients in moderate stages of dementia. Data regarding medication were not available from all centres. Information concerning the use of cholinesterase inhibitors was recorded from 1,738 patients (61.9%), of whom 1,255 (72.2%) used it. In addition, use of antipsychotics was recorded from 1,157 patients (41.2%), to 97 (8.4%) of whom it was prescribed.

Apathy was the most common symptom, being clinically present in 56% of the patients. Anxiety and depression were also very common, being present in about 37% of the patients.

Factor Analyses

The results of the factor analysis of the total patient group are shown in table 1. Principal component analysis (Varimax rotation), using the criterion of eigenvalues >1,

Table 2. Factor analyses for different dementia subtypes: AD (n = 2,354) versus other diagnosis (n = 454: total group n = 2,808); and in addition separately for vascular dementia (n = 152) and Lewy body disease (n = 134)

Subsyndromes	AD	Other	Vascular	Lewy body
Hyperactivity				
Agitation	0.700	0.537	0.684	0.857
Euphoria	0.359	0.703	0.627	
Disinhibition	0.682	0.646	0.624	0.440
Irritability	0.707	0.572	0.685	0.855
Aberrant motor behaviour	0.432			
Psychosis				
Delusions	0.707	0.768	0.737	0.827
Hallucinations	0.808	0.822	0.788	0.887
Night-time disturbances	0.510	0.513	0.423	0.520
Aberrant motor behaviour		0.542	0.646	
Affective				
Depression	0.728	0.651	0.662	0.767
Anxiety	0.706	0.754	0.811	0.754
Apathy				
Apathy	0.629	0.678	0.713	0.722
Eating abnormalities	0.705	0.775	0.808	0.633
Aberrant motor behaviour				0.612
Other				
Euphoria				0.931

Factor loading ≥0.40.

reduced the 12 symptoms to 4 factors. The 4 factors explained 52.3% of the total variance in the data. The first factor (23.3% of the total variance) denoted a dimension representing 'hyperactivity' and had high loadings on agitation, euphoria, disinhibition, irritability and aberrant motor behaviour. The second factor (10.6% of the total variance) represented a 'psychosis' dimension, including delusions, hallucinations and night-time behaviour disturbances. The third factor (9.4% of the total variance) represented an 'affective' dimension and had high loadings on depression and anxiety. The fourth factor (9.1% of the total variance) represented an 'apathy' dimension and had high loadings on apathy and appetite and eating abnormalities.

The analysis for patients with AD (n = 2,354) revealed a factor structure analogous to that found for the total patient group (table 2). More details about these analyses can be found in a previous article of our group [3]. A subanalysis including all patients with a diagnosis other than AD (n = 454) resulted in a similar factor structure, but aberrant motor behaviour was not included in factor 1 hyperactivity but in factor 2 psychosis. The same was the case for a subanalysis including only patients with vascular dementia (n = 152). In patients with Lewy body dementia (n = 134) 'euphoria' was a separate factor, and aberrant motor behaviour was not included in factor 1 hyperactivity but in factor 4 apathy. Reliable subanalyses of the other diagnostic groups could not be done because of the relatively small sample sizes. These results implied that for dementia subtype the 4-factor structure was relatively consistent across AD dementia, vascular dementia, dementia with Lewy bodies and in a broad group of patients with other dementia.

Subanalyses with regard to gender showed that the factor structure based on the data from only males (n = 952) resembled that of the total group, but again aberrant motor behaviour shifted to factor 2 psychosis. Night-time behaviour disturbances did not reach the criteria of a factor loading ≥ 0.40. In females (n = 1,856), the same factor structure of the total group emerged, but night-time behaviour disturbances had high loadings on both factor 2 psychosis and factor 4 apathy. Therefore, gender was not of large influence on the factor structure, showing the consistent presence of the 4 factors as found in the total group.

In table 3 the results from the factor analyses for the other different subanalyses are shown. Separate analyses were performed for patients with mild (MMSE score >20; n = 1,015), moderate (MMSE score between 20 and 11; n = 1,434) and severe (MMSE scores ≤ 10; n = 359) dementia. They resulted in only slightly different factor structures for mild and moderate dementia. In mild dementia, aberrant motor behaviour had high loadings on both factor 1 hyperactivity and factor 4 apathy, and night-time behaviour disturbances was included in factor 3 affective symptoms. In moderate dementia aberrant motor behaviour was included in factor 4 apathy. In severe dementia the factor structure was significantly different from the other groups. The symptoms included in factor 1 hyperactivity and factor 2 psychosis were combined in the same factor, however, euphoria and aberrant motor behaviour could not be included in one of the other factors. Night-time behaviour disturbances had the highest correlation with the factor apathy. The results showed that the 4 factors remained relatively consistent across patients with mild to moderate dementia but that the factor psychosis disappeared in patients with severe dementia.

A reliable subanalysis of data from only the youngest (40–65 years; n = 262) patients could not be performed because the rotation procedure of the factor analysis failed to converge in several iterations (probably because

Table 3. Factor analyses for different subsamples (factor loading ≥0.40)

Sub-syndromes	Age years		MMSE			Cholinesterase inhibitors		Antipsychotics no (n = 1,060)
	66–75 (n = 850)	76–99 (n = 1,696)	>20 (n = 1,015)	20–11 (n = 1,434)	≤10 (n = 359)	yes (n = 1,255)	no (n = 483)	
Hyperactivity								
Agitation	0.758	0.639	0.576	0.635	0.635	0.666	0.748	0.706
Euphoria		0.564	0.668	0.534				0.436
Disinhibition	0.541	0.697	0.726	0.668	0.684		0.737	0.670
Irritability	0.736	0.653	0.538	0.625	0.683	0.677	0.733	0.704
Aberrant motor behaviour		0.465	0.424			0.520	0.538	0.452
Delusions					0.710			
Hallucinations					0.700			
Apathy						0.491		
Eating abnormalities						0.403		
Psychosis								
Delusions	0.771	0.698	0.700	0.722		0.706	0.821	0.620
Hallucinations	0.773	0.820	0.842	0.820		0.745	0.843	0.693
Night-time disturbances		0.560		0.455				0.668
Aberrant motor behaviour	0.414							
Affective								
Depression	0.591	0.778	0.718	0.729	0.726	0.721	0.683	0.727
Anxiety	0.563	0.785	0.739	0.761	0.822	0.715	0.758	0.629
Night-time disturbances			0.434			0.469	0.483	
Euphoria	–0.583							
Apathy								
Apathy	0.639	0.681	0.783	0.606	0.648		0.647	0.633
Eating abnormalities	0.726	0.702	0.479	0.732	0.718		0.726	0.732
Aberrant motor behaviour				0.498				
Night-time disturbances	0.506				0.648			
Other								
Euphoria					0.831	0.868	0.837	
Aberrant motor behaviour					0.542			
Disinhibition						0.647		

of the small sample size). In patients with middle age (66–75 years; n = 850) night-time behaviour disturbances had high factor loadings on both factor 2 psychosis and factor 4 apathy, whereas aberrant motor behaviour was included in factor 2 psychosis. The factor structure of the oldest (76–99 years; n = 1,696) subgroup was similar to the total group. These results implied that the 4 factors were relatively consistent across age, however, no conclusions could be drawn for patients with early-onset dementia.

Finally, subanalyses were performed for use of cholinesterase inhibitors (yes: n = 1,255) and antipsychotics (yes: n = 97). Only patient data from whom information regarding use of these medications was available were used. Patients using no cholinesterase inhibitors had a factor structure similar to the total group, but night-time behaviour disturbances were included in factor 3 affective symptoms and euphoria was a factor on its own. The factor structure of patients using cholinesterase inhibitors was significantly different from those who did not. The factors 1, hyperactivity, and 4, apathy, were combined into 1 factor, but euphoria and disinhibition were a combined factor on their own. Again night-time behaviour disturbances were included in factor 3 affective symptoms. These data showed that use of cholinesterase inhibitors had influence on the factor structure, in which the factor apathy was included in the factor hyperactivity. Patients using no antipsychotics had the same factor structure as the total group. However, reliable subanalyses of patients using antipsychotics could not be performed because of the small sample size.

Discussion

The aim of the present study was to examine the consistency of neuropsychiatric syndromes among several subgroups by analyzing a large dementia population. The same subsyndromes as reported recently were found, representing the 4 subsyndromes hyperactive behaviours, psychosis, affective behaviours and apathy [3]. It is of main interest that these subsyndromes remained relatively consistent when analyses were performed separately for several dementia subtypes, e.g. AD, vascular dementia and dementia with Lewy bodies. Each of the 4 factors had at least 2 symptoms that remained consistent across the various analyses, implying shared biological mechanisms or shared environmental factors. However, the attribution of the symptoms aberrant motor behaviour and night-time behaviour disturbances to one of the syndromes tended to be less consistent, indicating poor specificity for one single dimension. Moreover, the factor structure, e.g. presence of the 4 subsyndromes, was only dependent on dementia severity and cholinesterase inhibitor use but not on dementia subtype, age and gender.

The inclusion of night-time behaviour disturbances in the psychosis factor is in accordance with findings of Schreinzer et al. [24], who found a factor representing diurnal rhythm disturbances and hallucinations. They concluded that their factor did not fulfil the criteria for delirium but nevertheless implied that it was of clinical importance because these symptoms require specific treatment strategies.

The co-occurrence of aberrant motor behaviour with psychosis in the same factor was also found by Matsui et al. [5]. Moreover, they reported that their psychosis factor included a larger number of NPI symptoms, including all symptoms (but euphoria) in our hyperactive behaviours subsyndrome. They concluded that, as dementia progresses, psychosis may frequently coexist with agitated behaviours. This is in line with our finding that in severely demented patients psychosis and hyperactivity more often co-occurred than in less severely impaired patients. The explanation of Matsui et al. [5] for the co-occurrence of psychosis and hyperactive behaviours was that psychosis may worsen executive dysfunctions, resulting in problems with, for example, personal inter-relationships, finally leading to hyperactive behaviours. Several previous studies have also found correlations between psychosis and agitated behaviours, resembling the hyperactive subsyndrome found in the present study [25–27].

One of the strenghts of the present study was that a large number of patients with different dementia subtypes (AD, vascular dementia and Lewy body disease) were included for separate analyses, resulting in a relatively consistent presence of subsyndromes. To our knowledge no previous studies on the presence of neuropsychiatric subsyndromes including such a high number of patients with vascular dementia or Lewy body disease have been performed. Nevertheless, future studies are necessary before definite answers can be given regarding the presence of neuropsychiatric subsyndromes of other dementia subtypes, like frontal-temporal dementia. A limitation of the present study was that neuropsychiatric symptoms were only assessed by the NPI. Future studies should also include non-NPI symptoms, such as shouting, changes in personality and changes in sexual behaviour, because these may contribute to the variety of neuropsychiatric patterns in dementia and inclusion of these symptoms may identify other subsyndromes. Secondly, no clear conclusions could be drawn about the influence of cholinesterase inhibitors and antipsychotics on the structure of the subsyndromes because medication data were not available from all patients. In our study, use of cholinesterase inhibitors influenced the outcome of the apathy factor in particular, being included in the hyperactivity subsyndrome. This may be explained by the neuropsychiatric effects of cholinesterase inhibitors. Clinicians often prescribe cholinesterase inhibitors for delirium-related symptoms, including presence of agitation and apathy [28, 29]. Previous studies with the cholinesterase inhibitors donepezil, galantamine and rivastigmine have suggested that these drugs reduce neuropsychiatric symptoms, with apathy showing the most consistent gains [30, 31]. Nevertheless, a recent review of the treatment of neuropsychiatric symptoms of dementia concluded that, although some trials of cholinesterase inhibitors have shown statistically significant effects, these effects have been small and of questionable clinical significance [32].

In the present study, some methodological issues need to be considered. Several subanalyses were performed for dementia subtypes, gender, age, dementia severity, and use of cholinesterase inhibitors and antipsychotics. This raises a multiple testing problem. Therefore, a post-hoc test-retest was performed by a randomized split-sample approach. Again, for both subsamples the same factor structure was found as for the total group, confirming the robustness of the findings. Secondly, when interpreting the results of the present study, one has to realize that the data are derived from a multi-centre study, implying

some methodological issues. Inter-centre and inter-country differences in terms of distribution of risk factors (e.g. age, gender, dementia subtype, dementia severity and medication use), differences in the distribution of NPI scores, but also differences in the quality of the information obtained from the informant, can affect the factor structure. However, post-hoc analyses were performed on the dataset excluding centres or countries, but this resulted in factor structures analogous to those found for the total patient group. Because of the retrospective nature of the study it was not possible to correct for the several possible methodological issues related to multi-centre studies, however, the EADC is a network of European centres of excellence specializing in dementia, and good clinical practice therefore can be assumed. Nevertheless, future prospective multi-centre studies might be of interest to rule out possible related methodological issues and to focus on cultural differences in particular.

Overall, it can be concluded that the present study found evidence of the relative consistency of 4 neuropsychiatric subsyndromes across several clinical and demographic subgroups of patients with dementia. The factor structure was relatively independent of dementia subtype, age and gender but was dependent on dementia severity and cholinesterase use. In particular, the subsyndromes hyperactivity and affective behaviours were present in all subgroups, but the presence of the subsyndromes apathy and psychosis was dependent on cholinesterase use and severe dementia, respectively. Future studies, specifically including dementia patients with other dementia subtypes like frontal-temporal dementia, early-onset dementia and patients in the severe stages of the disease, are needed before definite answers can be given regarding the presence of subsyndromes. In addition, the influence of psychotropic medication and in particular cholinesterase inhibitors and antipsychotics on the presence of subsyndromes deserves further study.

Our study provided evidence of the relative consistence of neuropsychiatric subsyndromes in dementia. This may strengthen the intention of researchers and clinicians to be alert to the presence of these subsyndromes, instead of just paying attention to individual symptoms. In addition, the subsyndromes can give insight into possible relationships between neuropsychiatric symptoms and their underlying cause and risk factors. Furthermore, interventions might be more effective when targeting subsyndromes rather than individual symptoms.

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