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Neuropsychiatric Syndromes in Dementia

Results from the European Alzheimer Disease Consortium: Part I

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Key Words
Neuropsychiatric syndromes · Neuropsychiatric Inventory · Factor analysis · Alzheimer's disease · Dementia · Subsyndromes

Abstract

Background/Aims: The aim of this study was to identify neuropsychiatric subsyndromes of the Neuropsychiatric Inventory in a large sample of outpatients with Alzheimer's disease (AD). ***Methods:*** Cross-sectional data of 2,354 patients with AD from 12 centres from the European Alzheimer's Disease Consortium were collected. Principal component analysis was used for factor analysis. ***Results:*** The results showed the presence of 4 neuropsychiatric subsyndromes: hyperactivity, psychosis, affective symptoms and apathy. The subsyndrome apathy was the most common, occurring in almost 65% of the patients. ***Conclusion:*** This large study has provided additional robust evidence for the existence of neuropsychiatric subsyndromes in AD.

Introduction

Neuropsychiatric symptoms, previously denominated as behavioural and psychological symptoms of dementia, are being increasingly recognized as an important aspect of dementia because of their impact on the quality of life of both patients and their caregivers. In recent years, several studies have been conducted with the aim of determining neuropsychiatric subsyndromes in patients with dementia. The study of neuropsychiatric subsyndromes instead of separate neuropsychiatric symptoms is impor-

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Table 1. Results of previous factor analytic studies using the NPI

Authors	Patients	Mean MMSE score	NPI items	Factors
Frisoni et al. [7], 1999	162	13.3	10	mood/frontal/psychosis
Fuh et al. [16], 2001	95	12.7	12	mood-psychosis/psychomotor regulation/social engagement
Aalten et al. [1], 2003	199	18.1	12	mood-apathy/psychosis/hyperactivity
Spalletta et al. [17], 2004	244	17.5	10	mood-excitement/mood-depression-apathy/psychosis/hyperactivity/anxiety
Benoit et al. [6], 2003	244	23.4	10	psychosis-agitation/mood/hallucination
Mirakhur et al. [13], 2004	435	13.0	12	affect/physical/psychosis/hypomania
Matsui et al. [18], 2006	140	20.3	10	mood/psychosis/euphoria

NPI = Neuropsychiatric Inventory; MMSE = Mini Mental State Examination.

tant for several reasons. A large amount of data support the notion that behavioural and psychological symptoms of dementia is not a unitary concept but should rather be considered as groups of symptoms, each reflecting a different prevalence, course over time, biological correlates and psychosocial determinants [1, 2]. Furthermore, the identification of subsyndromes may point to a common neurobiological pathogenesis, or may react to the same treatment. Pharmacological studies have shown that treatments have an effect on behavioural aspects in dementia when studying neuropsychiatric subsyndromes but not when studying individual symptoms [3–5].

Most of these studies used factor analytic techniques [1, 6–13] to identify the subsyndromes, or cluster analysis [14, 15] to identify symptom clusters. Although these studies differ somewhat among themselves due to the use of different designs, assessment tools and the size of samples, there is also a degree of concordance between the neuropsychiatric syndromes found (table 1). This is particularly the case for the distinction in the subsyndromes hyperactivity, apathy/mood and psychosis, as has been proposed in the Maastricht Study of Behaviour in Dementia and several other studies [1, 2]. The question of whether depression and apathy belong to the same syndrome or are specific neuropsychiatric symptoms in their own right has been a matter of continuous debate. Some studies found depression and apathy to be integrated into the same subsyndrome [1, 7, 17–19], whereas others did not [13, 16].

The aim of the present study was to identify neuropsychiatric subsyndromes of the Neuropsychiatric Inventory (NPI) in a relatively large homogeneous sample of patients with dementia from several centres from the European Alzheimer's Disease Consortium (EADC). This article, produced by the behavioural subgroup of the EADC, aims to come to a more robust conclusion about the presence of neuropsychiatric subsyndromes in patients with dementia compared with previous studies by including the largest number of patients with Alzheimer's disease (AD) in this topic until now.

Methods

Patients

Patient data were collected by pooling several 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 (Réseau sur la maladie d'Alzheimer français) 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 [2]. 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). Only patients with the clinical diagnosis of AD were selected for the present study, resulting in the inclusion of 2,354 patients (85.5% of the total sample). Some centres contributed data about a relatively large number of patients. Studies encompassing >300 patients were Toulouse (Impact of Cholinergic Treatment Use, the ICTUS study, 491 patients), the REAL-FR dataset (488 patients) and a study from Perugia, Italy (586 patients). Ethical approval for data collection was obtained by each centre.

Neuropsychiatric Inventory

All studies used the NPI for the assessment of neuropsychiatric symptoms [20], a retrospective (up to 1 month) informant-based rating scale for psychopathology in patients with dementia.

The current version [21] 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, inter-rater reliability and test-retest reliability of the NPI have been established [22].

In line with previous studies, a score >3 was taken to indicate the presence of 'clinically relevant' symptoms [23–27]. The 12-item NPI was available for 2,188 patients (92.9%) 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, 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 clinical dementia diagnosis, use of cholinesterase inhibitors (yes-no) and antipsychotics (yes-no). The Mini Mental State Examination [28] was used as a global measure of cognitive functioning.

Statistical Analysis

Statistical analysis was performed with SPSS, version 12. A principal component analysis was performed on all 12 NPI items to detect neuropsychiatric syndromes, using an orthogonal rotational procedure (Varimax). Factors were selected on the basis of eigenvalues >1. Factor loadings ≥0.40 were included. Cronbach's α coefficients were used to assess the internal consistency of the factors. In addition, in order to test for the robustness of the data, several factor analytic techniques (direct oblimin, Quartimax, Equamax and Promax rotation) were compared.

Results

Characteristics of the Patients

The study included 745 men (31.6%) and 1,609 women (68.4%). The mean age was 76.7 ± 7.8 years (range = 40–97). The average Mini Mental State Examination score was 17.8 ± 5.9 (range = 0–29), indicating on average the inclusion of patients in moderate stages of dementia. Data regarding medication were not available from all centres, but information about the use of cholinesterase inhibitors and antipsychotics was recorded from 1,616 (68.6%) and 1,053 (44.7%) patients, respectively. Of these groups of patients 1,228 (76.0%) used cholinesterase inhibitors and 84 (8.0%) antipsychotics.

Apathy was the most common symptom, being clinically present in 55% of the patients (table 2). Anxiety and depression were also very common, occurring in about 37% of the patients. The rarest symptoms were euphoria (4.9%), hallucinations (9.1%) and disinhibition (9.5%).

Table 2. Mean NPI scores (severity × frequency: range = 0–12) and percentage of patients with symptoms

NPI items	Mean and SD	Patients with symptom (score >3)	
		%	n
Delusions	1.5 ± 2.8	19.4	457
Hallucinations	0.7 ± 2.1	9.1	213
Agitation	2.3 ± 3.1	31.1	732
Depression	2.8 ± 3.4	36.7	863
Anxiety	2.7 ± 3.3	37.0	871
Euphoria	0.4 ± 1.4	4.9	115
Apathy	4.2 ± 3.8	55.2	1,299
Disinhibition	0.8 ± 2.2	9.5	224
Irritability	2.4 ± 3.1	32.1	756
Aberrant motor behaviour	2.0 ± 3.4	27.5	647
Night-time behaviour disturbances	1.5 ± 2.9	19.5	427
Appetite and eating abnormalities	1.7 ± 3.2	21.8	477

Factor Analyses

The results of the factor analysis of the total patient group are shown in table 3. Principal component analysis (Varimax rotation), using the criterion of eigenvalues >1, reduced the 12 symptoms to 4 factors. The 4 factors explained 51.8% of the total variance in the data. The first factor (23.1% of total variance) denoted a dimension representing 'hyperactivity' and had high loadings on agitation, disinhibition, irritability and aberrant motor behaviour. Euphoria also had the highest loading on this factor but just failed to reach the threshold of loadings ≥0.40. The second factor (10.5% of the total variance) represented a 'psychosis' dimension, including delusions, hallucinations and night-time behaviour disturbances. The third factor (9.3% of the total variance) represented an 'affective' dimension and had high loadings on depression and anxiety. The fourth factor (8.9% of the total variance) represented an 'apathy' dimension and had high loadings on apathy, and appetite and eating abnormalities. The same factors emerged when different methods of rotation were used. However, comparable factor loadings on different factors were found for the symptoms aberrant motor behaviour and night-time behaviour disturbances. The loading of aberrant motor behaviour on

Table 3. Factor analysis of the NPI

	Factor 1: hyperactivity	Factor 2: psychosis	Factor 3: affective	Factor 4: apathy
Delusions	0.294	*0.707*	0.063	–0.018
Hallucinations	0.134	*0.808*	0.054	–0.011
Agitation	*0.700*	0.112	0.274	0.036
Depression	0.069	0.052	*0.728*	0.206
Anxiety	0.154	0.141	*0.706*	0.023
Euphoria	*(0.359)*	0.049	–0.355	0.207
Apathy	0.121	–0.141	0.184	*0.629*
Disinhibition	*0.682*	0.139	–0.119	0.030
Irritability	*0.707*	0.093	0.278	0.026
Aberrant motor behaviour	*0.432*	0.222	–0.118	(0.412)
Night-time behaviour disturbances	–0.054	*0.510*	0.157	(0.431)
Appetite and eating abnormalities	0.000	0.105	–0.011	*0.705*
Eigenvalues	2.772	1.264	1.117	1.063
Variance, %	23.10	10.54	9.31	8.86

Italics indicate factor loading ≥0.40. Parentheses indicate factor loading just below criterion ≥0.40.

Table 4. Description of the 4 NPI factors

Outcome	Factor score		Patients in factor (frequency × severity >3)		NPI total score for patients in factor	
	mean	range	n	%	mean	range
Hyperactivity (n = 2,354)	7.9	0–60	1,498	63.6	28.5	4–128
Psychosis (n = 2,188)	3.8	0–36	829	37.9	33.7	4–128
Affective (n = 2,354)	5.6	0–24	1,387	58.9	27.4	4–128
Apathy (n = 2,188)	5.8	0–24	1,415	64.7	27.0	4–128

Psychosis: n = 2,188; the 12-item NPI (including sleep and eating disturbances) was available for 2,188 patients.

the hyperactivity factor was 0.43 and on the apathy factor 0.41. In addition, a reliability analysis revealed that if aberrant motor behaviour was omitted from the factor hyperactivity, the Cronbach's α coefficient decreased from 0.60 to 0.58. Therefore, aberrant motor behaviour was included in the factor hyperactivity. If night-time behaviour disturbances were omitted from the factor psychosis, the Cronbach's α coefficient increased somewhat (from 0.51 to 0.58), but taking into account its high loading (0.51) on this factor, it was decided not to remove this symptom from the factor.

The descriptions of the 4 factors are given in table 4. The factor scores are based on the summed NPI scores for each factor. The most common subsyndrome was the apathy subsyndrome (65%), followed by the hyperactivity (64%), affective (59%) and psychosis (38%) subsyndromes. The patients with the psychosis subsyndrome had the highest mean NPI total score. The combination of a clinically significant presence of the hyperactivity and psychosis subsyndromes was present in 28% of the patients. Hyperactivity and affective occurred in 38% of the patients, hyperactivity and apathy in 42%, psychosis and affective in 24%, psychosis and apathy in 25%, and 37% of the patients had a score of ≥4 on both affective and apathy.

Discussion

The aim of the present study was to come to a robust conclusion regarding the presence of neuropsychiatric syndromes by analyzing the largest dementia population ever studied for this purpose. The data showed the presence of 4 factors, explaining 52% of the variance; high eigenvalues were found in all 4 segregated factors. Although the exact labelling of the factors can be an issue for discussion, the factor analysis resulted in the 4 neuropsychiatric subsyndromes hyperactive behaviours, psychosis, affective behaviours and apathy. These are in line with the labels proposed by previous studies [1, 2]. Most symptoms had high factor loadings, thus giving support to the differentiation of the 4 subsyndromes. The most common subsyndrome was apathy. The psychosis subsyndrome was less prevalent but was associated with the highest level of total neuropsychiatric problems.

The factor structure of the present study was surprisingly similar to that published earlier by Aalten et al. [1]. However, one important difference was the separation of apathy from depression in the present study, implying an independent factor. This is in line with what is recognized in daily practice and postulated by several authors and previous studies [13, 16, 29, 30]. Nevertheless, most previous studies using the NPI have not been able to distinguish the 2 syndromes of depression and apathy [7, 17–19]. The question of whether depression and apathy are distinct syndromes has been the topic of considerable discussion and remains controversial. The symptoms of apathy may be mistaken for those of depression because both apathy and depression can manifest themselves as diminished interest, slowing and lack of energy. Although lack of motivation occurs in apathy and depression, apathy denotes a lack of motivation without dysphoria. Future research is still necessary to increase our understanding of the differentiation between depression and apathy. These studies could be improved by the use of specific measurements that permit a greater distinction between these 2 syndromes, such as the 'apathy inventory' [31].

The findings with regard to the factors hyperactivity and psychosis are largely consistent with the previous studies, as listed in table 1. However, the attribution of the symptoms aberrant motor behaviour and night-time behaviour disturbances to one of the subsyndromes is less clear. In this study, aberrant motor behaviour had high loadings for the subsyndromes hyperactivity and apathy but seemed to fit better in the former. Likewise, night-time behaviour disturbances had high loadings on the psychosis and apathy subsyndromes, but it was decided to include them in the factor psychosis. The inclusion of night-time behaviour disturbances in the psychosis factor is in accordance with the findings of Schreinzer et al. [12], 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 it was of clinical importance because these symptoms require specific treatment strategies.

The present study has several strengths. Firstly, this is a study of a very large sample. Moreover, this is the first study that only included patients with at least 1 clinically relevant NPI symptom, i.e. a score >3. By doing this, the results were not biased by the inclusion of patients without any symptom or clinical relevance, resulting in less variance of the data. Furthermore, the robustness of the subsyndromes was confirmed because no changes occurred in factor structures when different methods of rotation were used. There is no consensus about which instrument should be used for the assessment of neuropsychiatric symptoms in dementia. Nowadays the NPI is regarded as the gold standard for determining the presence of neuropsychiatric symptoms in several neurodegenerative diseases. Nevertheless, we are aware that the NPI is limited by the scoring of just 12 common symptoms, not taking into account non-NPI symptoms like shouting, hoarding and change in personality. It will therefore be of interest to study factor structures of neuropsychiatric symptoms as assessed by the NPI and other specific scales for particular problems.

This study also had some limitations. It included only patients with AD. This implies that the results cannot necessarily be generalized to dementias with other aetiologies. Another limitation is that we did not have data available for all patients concerning the treatment they used. The majority of the patients already used cholinesterase inhibitors at the time of data collection, so it is not a naturalistic study. However, the group represents the real population studied in Europe. In addition, the present article did not perform subanalyses regarding severity of dementia, gender, age and use of medication, because of the clearness of the analyses and article. However, we are aware that when interpreting and using subsyndromes of dementia one has to realize that different factor structures may appear when checking for these variables. In this respect, a following study of the EADC data will go into more detail regarding these subanalyses.

The present study has provided additional evidence for the presence of neuropsychiatric subsyndromes in dementia, as defined by the NPI. Nevertheless, the debate about the definition of the several psychiatric and behavioural symptoms in dementia is continuing. Moreover, the acknowledgement of the presence of neuropsychiatric syndromes can be seen from the increase in publications using neuropsychiatric syndromes in their analyses rather than isolated symptoms. Neurobiological correlates of neuropsychiatric symptoms in dementia have been found that support the existence of neuropsychiatric subsyndromes [2].

It can be concluded that the present study provides additional evidence for the existence of 4 neuropsychiatric subsyndromes in AD, corresponding to hyperactive (agitated) behaviours, psychosis, affective behaviours and apathy. These neuropsychiatric syndromes can give insight into possible relationships between clinical features and their underlying causal and/or risk factors. Besides, different therapeutic strategies may be more effective when targeting subsyndromes rather than individual symptoms. The conclusions from this large EADC dataset will lead to consensus about the presence of neuropsychiatric syndromes and allow future substudies related to this topic.

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