ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-9

Alzheimer's & Dementia

Featured Article

The stability of neuropsychiatric subsyndromes in Alzheimer's disease

Michael H. Connors[a,b], Katrin M. Seeher[a,b], John Crawford[b], David Ames[c,d], Michael Woodward[e], Henry Brodaty[a,b,*]

[a]*Dementia Centre for Research Collaboration, UNSW Sydney, Sydney, Australia*
[b]*Centre for Healthy Brain Ageing, UNSW Sydney, Sydney, Australia*
[c]*National Ageing Research Institute, Melbourne, Australia*
[d]*Academic Unit for Psychiatry of Old Age, University of Melbourne, Melbourne, Australia*
[e]*Austin Hospital, Heidelberg, Australia*

Abstract

Introduction: Neuropsychiatric symptoms are common in Alzheimer's disease. Previous research has attempted to identify subsyndromes—sets of symptoms related to one another—to clarify underlying mechanisms and treatment targets. We examined the stability of these subsyndromes over time.
Methods: We administered the Neuropsychiatric Inventory annually for 3 years to 447 patients with Alzheimer's disease recruited from memory clinics. We conducted principal component analyses at each time point and multigroup confirmatory factor analyses across time.
Results: Principal component analyses showed that no two time points shared the same factor structure. Factor solutions did not exhibit strong simple structures, and substantial cross-loadings were common. Confirmatory analysis revealed significant differences in factor loadings and model fit over time.
Discussion: Symptoms cannot be neatly partitioned into discrete clusters that are stable over time. The findings highlight the significant challenges that clinicians and caregivers face and may help explain the lack of success in intervention studies.

Keywords: Alzheimer's disease; Behavioral and psychological symptoms of dementia; Dementia; Factor analysis; Longitudinal; Neuropsychiatric symptoms; Neuropsychiatric subsyndromes; Neuropsychiatric Inventory

1. Introduction

Most patients with Alzheimer's disease (AD) experience neuropsychiatric symptoms (NPSs) during the course of their illness [1]. These symptoms include depression, anxiety, apathy, agitation, disinhibition, motor disturbances, delusions, and hallucinations. Approximately 80% to 90% of patients exhibit at least one NPS [1,2]. Most have multiple symptoms, with around half experiencing four or more [3].

The study was funded in part by Janssen-Cilag Pty Limited. Janssen-Cilag had no input into the design, execution, analysis, interpretation, or writing of this study. K.M.S., M.W., and H.B. have worked on drug trials for patients with mild cognitive impairment and Alzheimer's disease sponsored by major pharmaceutical companies including Eisai Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, H Lundbeck A/S, Janssen-Cilag, Medivation Inc., Merck Sharp and Dohme, Novartis Pharmaceuticals, Nutricia, Pfizer Inc., Prana Biotechnology, Sanofi-Aventis, Servier, Tau Therapeutics, Voyager Pharmaceutical Corporation, and Wyeth Limited. M.W. has also worked on trials sponsored by AbbVie, Biogen, the Buck Institute, Forest, Takeda, and vTv Therapeutics. H.B. has been a consultant, advisory board member, or sponsored speaker for Nutricia, Tau Therapeutics, Servier, and Sanofi. M.W. has been a consultant and speaker for these companies as well as bioCSL, CogRx, Eli Lilly and Company, Merck Sharp and Dohme, Novartis, and Prana Biotechnology. DA has served as a paid consultant to Janssen-Cilag and received payment for consultancies from Baxter, Eli Lilly, Lundbeck, Prana, Pfizer, and Novartis. M.H.C., and J.C. have no conflicts of interest to declare.

*Corresponding author. Tel.: (+61 2) 9385 2585; Fax: (+61 2) 9385 2200.
E-mail address: h.brodaty@unsw.edu.au

https://doi.org/10.1016/j.jalz.2018.02.006
1552-5260/

As a result, research has focused on identifying subsyndromes—sets of symptoms that are related to one another—to help clarify underlying causal mechanisms [1,4–6]. If such NPS groupings were consistent and pointed to shared underpinnings, they could also suggest common therapeutic interventions [7–10]. As such, the study of neuropsychiatric subsyndromes has been classed as an area of importance by the Alzheimer's Association [6,8,11], European Alzheimer's Disease Consortium [10], and US Food and Drug Administration [12].

Previous research has identified subsyndromes by administering surveys of NPSs—usually the Neuropsychiatric Inventory (NPI)—and conducting factor analyses on the responses. This approach typically reveals three or four main groups of symptoms [1,9,13]. An early study [14] identified three factors: hyperactivity (agitation, euphoria, irritability, disinhibition, aberrant motor behavior), mood/apathy (depression, apathy, night time disturbances, appetite/eating abnormalities), and psychosis (delusions, hallucinations, anxiety). In another study [15], the same authors identified four factors with a slightly different structure. Similar, though not identical, factors were apparent in patients with different levels of dementia severity, suggesting that subsyndromes may be stable over time. Inspection of the different factor solutions across other studies also reveals common patterns, with certain symptoms tending to have major loadings on the same factor more frequently than others [9]. Nevertheless, there is noticeable variation in the number and composition of factors identified across more than 25 studies. A systematic review of neuropsychiatric subsyndromes in AD found that no two previous studies reported exactly the same factor composition [13].

A significant limitation of previous research is that it has only rarely examined the stability of subsyndromes over time in the same individuals [13]. Most studies performed cross-sectional factor analyses. This is problematic because the prevalence and trajectory of individual symptoms that constitute the factors vary across the disease's course [1,3,16]. Five studies [17–21] attempted to address this issue by repeating factor analyses at different time points within a longitudinal design. These studies concluded that factor structures remained relatively stable, although some symptoms changed the factors on to which they loaded. Only one of these studies, however, used confirmatory factor analysis [17], and none statistically tested the structural equivalence of their factor solutions over time. In addition, these studies did not control for dementia severity, identified different compositions of factors to each other, and observed different symptoms to change the factor on which they mainly loaded over time. It is thus unclear whether the identified factors are truly stable. Given the inconsistent findings in both cross-sectional and longitudinal studies, it is also unclear whether it is appropriate to describe the relationships between NPSs in terms of distinct nonoverlapping subsyndromes; that is, groups of symptoms with relatively high intercorrelations and lower correlations with symptoms belonging to different subsyndromes.

We examined the nature and stability of relationships between neuropsychiatric subsyndromes over 3 years in a large sample of patients with AD. We focused on the 10-items in the original NPI scale (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior) as a systematic review found that this scale was more likely to produce stable subsyndromes than the 12-item version (which also assesses appetite and sleep disturbances) [13]. We conducted exploratory factor analyses at each time point and a multiple-group confirmatory factor analysis across time to test the stability of factor structures. Given the inconsistency in previous exploratory factor analyses [13], we tested the factor structure of an existing model [17] in the confirmatory analysis. This model is the only one to have been previously tested with confirmatory analysis over time, albeit without testing for structural invariance. In addition, the model's proposed subsyndromes—psychotic (delusions, hallucinations), emotional (agitation, irritability, depression, anxiety), and behavioral (disinhibition, euphoria, aberrant motor behavior, apathy)—are similar to other accounts and closely related to existing theoretical accounts [1,9]. We hypothesized that, if neuropsychiatric subsyndromes are stable entities, consistent groupings of NPSs would emerge in both exploratory and confirmatory analyses.

2. Methods

2.1. Design

Participants were drawn from the PRIME study [22], a 3-year observational study of patients attending memory clinics. Of 970 patients recruited, 781 had dementia (521 with the Alzheimer's type) and 189 had mild cognitive impairment. All patients received specialist assessment or treatment at one of nine memory clinics around Australia. Patients, together with a family member or friend as their informant, had annual follow-ups with a research nurse/psychologist or specialist clinician, with additional visits at 3 and 6 months (analyses in this study focused on annual visits). Ethics approvals were obtained from institutional ethics committees associated with individual referring centers (National Institute of Health clinical trials registry number: NCT00297271).

2.2. Participants

The present analyses focused on patients with AD. All had received a diagnosis from a specialist clinician according to DSM-IV criteria [23]. Patients were included in the Q2 PRIME study if they lived in the community, had less than 40 hours/week care, were fluent in English, had a caregiver consent to the study, and provided written informed consent either themselves or through a legal guardian/proxy. Patients with acute or life-threatening illness were excluded.