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A Multiple Indicators Multiple Causes (MIMIC) model of Behavioural and Psychological Symptoms in Dementia (BPSD)

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Abstract

Introduction: Although there is evidence for distinct behavioural sub-phenotypes in Alzheimer's disease (AD), their inter-relationships and the effect of clinical variables on their expression have been little investigated.
Methods: We have analysed a sample of 1850 probable AD patients from the UK and Greece with 10 item Neuropsychiatric Inventory (NPI) data. We applied a Multiple Indicators Multiple Causes (MIMIC) approach to investigate the effect of MMSE, disease duration, gender, age and age of onset on the structure of a four-factor model consisting of "psychosis", "moods", "agitation" and "behavioural dyscontrol".
Results: Specific clinical variables predicted the expression of individual factors. When the inter-relationship of factors is modelled, some previously significant associations are lost. For example, lower MMSE scores predict psychosis, agitation and behavioural dyscontrol factors, but psychosis and mood predict the agitation factor. Taking these associations into account MMSE scores did not predict agitation.
Conclusions: The complexity of the inter-relations between symptoms, factors and clinical variables is efficiently captured by this MIMIC model.

Keywords: Alzheimer's disease (AD); BPSD; Behavioural sub-phenotypes; Structural Equation Modelling (SEM); Confirmatory Factor Analysis (CFA); Multiple Indicators Multiple Causes (MIMIC) model; Factors; Latent variables; Differential Item Functioning (DIF); Neuropsychiatric Inventory (NPI); Covariates; MMSE; Disease duration; Age; Age of onset

1. Introduction

Behavioural and Psychological Symptoms in Dementia (BPSD) commonly occur in patients with Alzheimer's disease (AD). As many as 80% of patients with AD have one or more symptom of BPSD as measured using scales such as the Neuropsychiatric Inventory (NPI) (Craig et al., 2005; Drevets and Rubin, 1989; Finkel, 1996; Rosen and Zubenko, 1991). BPSD are strongly associated with more

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severe functional and cognitive decline (Craig et al., 2005; Cummings, 2000; Stern et al., 1994) and result in carer stress, premature institutionalisation, as well as increased social and economic cost (Donaldson et al., 1998; Steele et al., 1990).

However, little is known about the heterogeneity of BPSD observed in clinical practice. Several reports have addressed biological, clinical and demographic correlates associated with individual BPSD, but with little consistency. BPSD are diverse and symptoms fluctuate with time and it is therefore difficult to study their interactions. Some behavioural symptoms in AD tend to occur together suggesting that distinct behavioural sub-phenotypes exist. For example two large recent studies have identified, using exploratory factor analysis techniques, four sets of symptoms (latent variables or factors) that occur together (Aalten et al., 2007; Hollingworth et al., 2006). Such 'sub-phenotypes' may have distinct neurobiological correlates. If the molecular pathways responsible could be identified then this might lead to novel treatment strategies for BPSD, since related symptoms could respond to the same drugs (Aalten et al., 2003). This is important as treatments currently used for the management of BPSD have poor efficacy and serious side effects (Madhusoodanan et al., 2007).

Although a number of studies have examined the effect of clinical variables on individual BPSD (Aalten et al., 2005a; Craig et al., 2005; Eustace et al., 2002; Mega et al., 1996; Piccininni et al., 2005; Selbaek et al., 2007; Spalletta et al., 2004) only a 2-year longitudinal study (Aalten et al., 2005b) and a cross-sectional study (Hollingworth et al., 2006) have examined the effect of clinical variables on behavioural sub-phenotypes. In addition, although behavioural sub-phenotypes in dementia co-occur and influence each other, only Aalten et al. (2005b) has addressed their inter-relationships. As latent variables have no scale and are represented through indicator variables, in this case behavioural symptoms, it is subsequently difficult to assess the overall effect of covariates or their inter-relationship using standard χ^2 difference tests. There is therefore a need for more systematic statistical approaches to investigate these complex associations.

The aim of this analysis was to extend previous studies of BPSD and to generate a model which describes the effects of covariates on latent variables and the inter-relationships of latent variables. We have utilised three independent datasets comprising over 1800 probable AD patients ($n = 1850$) and used Multiple Indicators Multiple Causes (MIMIC) modelling, a special case of Structural Equation Modelling (SEM). MIMIC models provide a better insight into the correlations between symptoms, latent variables and covariates. They have the advantage of not only allowing the simultaneous detection of associations between the covariates and latent variables but also the detection of direct associations between covariates and symptoms, after controlling for the presence of latent variables. Although MIMIC models have been successfully applied in geriatric research (Gallo et al., 1994; Mast, 2004, 2005) and psychiatric studies (Agrawal and Lynskey, 2007; Chung et al., 2005; Gomez and Vance, 2008) they have not been previously applied to BPSD studies.

2. Materials and methods

2.1. Subject cohorts

We used three independently ascertained cohorts: the UK/Ireland cohort comprising 957 participants from the Medical Research Council Genetic Resource for Late-onset AD, a cohort of 348 participants from Queen's University Belfast (the Northern Irish Cohort) and a cohort from Greece with 545 participants from Thessaloniki (total number of patients: 1850). All individuals were unrelated white European, recruited through secondary care services and diagnosed with probable AD in accordance with the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's disease and Related Disorders Association clinical diagnostic criteria (McKhann et al., 1984). The Neuropsychiatric Inventory (NPI) (Cummings, 1997) was used to assess prevalence and severity of BPSD in participants. The NPI is an informant-based rating scale that evaluates 12 common behavioural symptoms in AD. Informants were a patient's caregiver familiar with the patient's behaviour. The severity of each symptom is rated from and 0 to 3 (does not occur, mild, moderate, and severe) and the frequency of symptoms is rated from 0 to 4 (never, less than once per week, about once per week, several times per week, and once or more per day). Frequency and severity scores are multiplied to give an overall domain score for each symptom ranging from 0 to 12. The NPI scores used here were collected at baseline interview and the product of frequency and severity was used to reflect the overall severity of each symptom over the duration of the illness. The reliability and validity of the NPI are well established, and it is commonly used in research and clinical settings (Cummings, 1997). All sites are experienced users of this scale. The 12-item NPI was used in the UK/Ireland and Northern Irish cohorts and either the 10 or 12 item NPI in the Greek cohorts. Sleep disturbances and appetite abnormalities were excluded from the analyses on this cohort. All patients had disease duration of 2.5 years or more. Ethical approval was obtained from the relevant ethical review boards.

2.2. Summary of statistical analyses

Structural Equation Modelling (SEM) analyses were conducted in Mplus Version 5.1 (Muthen and Muthen, 2006). The mean and variance-adjusted weighted least squares (WLSMV) extraction procedure was used. The WLSMV is a robust estimator which does not assume normally distributed variables and provides the best option for modelling categorical or ordered data (Brown, 2006). Initially, Confirmatory Factor Analysis (CFA) was performed on the merged dataset, consisting of 1850 AD patients, in order to establish

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a valid model prior to the addition of covariates. Multiple Indicators Multiple Causes (MIMIC) modelling was used to test the effects of covariates on a hypothesised four factors model. Disease duration, cognitive impairment as measured by the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (1 = MMSE scores 0–10, 2 = MMSE scores 11–20, 3 = MMSE scores 21–28), current age or age of onset (age and age of onset were strongly co-linear), gender and site (UK or Greece) were used as covariates in the MIMIC model. Hypotheses on the direction of the relationships between factors generated were tested. For all models tested a non-statistical significance of the χ^2-test relative to the degrees of freedom indicated that the implied theoretical model significantly reproduced the sample variance–covariance relationships in the matrix. As values are inflated by large sample sizes, model fit was also evaluated by using the root mean squared error of approximation (RMSEA). The RMSEA is one of the most informative criteria in covariance structure modelling and tests how well the model would fit the population covariance matrix if available. Values <0.05 indicate a very good model fit (Joreskog and Sorbom, 1996). The Comparative Fit Index (values >0.90 indicating a very good model fit) was also used. Modification Indices (MI), which are suggestions for paths that can be added to the model to improve goodness of fit, were included if they were >8 (MI > 3.84 for 1 degree of freedom are indicative of significant drop in the χ^2 if the path is freed) and whether they were acceptable from a theoretical standpoint. A detailed account of each methodological step is given below.

2.2.1. Multiple Indicators Multiple Causes (MIMIC) CFA

Prior to the addition of the covariates, Confirmatory Factor Analysis (CFA) was performed in order to establish a statistically accepted model. Since the sample used here contained almost 1000 of the same patients used by Hollingworth et al. (2006), their suggested principal component analysis model was used as a starting point. After the hypothesised model was evaluated and modified, covariates were added.

MIMIC modelling was used in order to assess the effect of covariates on the factor structure. The MIMIC model is a special case of SEM and consists of two parts; a measurement model which defines the relations between a latent variable and its indicators and a structural model which specifies the casual relationships among latent variables and explains the casual effects (Joreskog and Sorbom, 1996). The MIMIC model incorporates additional variables, which are assumed to influence the latent factors and also allows the testing of hypothesis on direction of effects between different factors. The MIMIC model can also include direct paths between the covariates and the factor indicators (i.e. NPI items). These direct paths indicate differences in the factor indicators (e.g. delusions) that can be attributed to the covariates (e.g. gender), after controlling for the factor (e.g. "psychosis" factor). In order to assess direct associations a stepwise forward model was used as proposed by Brown (2006). For each covariate a model with all paths towards the indicators (NPI items) constrained to zero was computed. The Modification Indices (MI) were then examined because they provide indication of how much the fit of the model would be improved if the paths were freely estimated. Higher MI indicates greater improvement. The path with the highest MI was freely estimated and a path from the covariate to this symptom is indicative of a significant association between the covariate and the symptom after controlling for the relevant latent variable. This process was repeated until all symptoms which were directly associated with the covariates were identified. After this, a significant effect of the covariate on the latent variable would imply differences on the latent mean score.

3. Results

The key demographic characteristics of the 1850 patients are presented on Table 1.

3.1. Confirmatory Factor Analysis

Confirmatory Factor Analysis (CFA) was applied to the merged dataset using the suggested four-factor solution reported by Hollingworth et al. (2006) as a starting point. The Northern Irish data set was previously used by Mirakhur et al. (2004) in a factor analytic study which presented similar results to Hollingworth et al. (2006). CFA overall verified the hypothesised factor structure, with some suggested modifications. This model suggested that disinhibition was also part of "agitation" factor. In addition, apathy belonged to the "behavioural dyscontrol" factor only and not in the "moods" factor. Four error covariances were drawn between the NPI items indicating relationships not captured by the current model and the final model had a good fit ($\chi^2 = 31.61$, df = 21, $p = 0.064$, RMSEA = 0.017, CFI = 0.997). Medium/high correlations between the four factors where observed. The highest correlation was observed between "behavioural dyscontrol" factor and "agitation", "moods" and "psychosis" factors ($\rho = 0.742$, $\rho = 0.674$ and $\rho = 0.654$, respectively). The lowest correlation was between "psychosis" and "moods" factors ($\rho = 0.442$), whereas medium correlations were observed between "agitation" and "psychosis" factors ($p = 0.558$) as well as between "agitation" and "moods" factors ($p = 0.535$). Results of the CFA model are presented in Supplementary Fig. 1, available online for the more interested reader.

3.2. Multiple Indicators Multiple Causes (MIMIC) model

Multiple Indicators Multiple Causes (MIMIC) modelling was used in order to assess the effect of covariates on the factor structure. MMSE, disease duration, age/age of onset, gender and site were used as covariates. We have also attempted to make specific hypothesises on the directions of

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Table 1
Basic demographic characteristics of the sample ($n = 1850$).

	Mean, median (standard deviation), range		
	UK site ($n = 1305$)	Greek site ($n = 545$)	Overall sample ($n = 1850$)
Age (years)	80.7, 81 (6.5), 63–99	75.4, 75 (5.4), 63–96	79.1, 79 (6.7), 63–99
Age at onset (years)	75.8, 75 (6.6), 60–94	70.1, 70 (5.7), 60–90	73.4, 73 (6.7), 60–94
Disease duration (months)	71.6, 60 (34.7), 30–192	64, 60 (30.1), 36–192	69.3, 60 (33.6), 30–192
MMSE score	11.3, 13 (9), 0–29	13.8, 14 (7.0), 0–29	12.7, 14 (8.5), 0–29
Females/males, %	70.6/29.4	65.3/34.7	68.9/31.1

the associations between the four factors. These hypotheses were based on the medium/high correlations between the four factors observed in the CFA model, on clinical observations and previously published work (Aalten et al., 2005b; Lopez et al., 2003; Rapoport et al., 2001). In more detail, since depressive symptoms appear early in the course of the disease (Craig et al., 2005) and have been reported to be correlated with aggressive symptoms (Aalten et al., 2005b) we hypothesised that "moods" factor could predict some of the variability of "agitation" factor. We have also hypothesised a bi-directional association between "moods" and "psychosis" factors since depressive and psychotic symptoms have been reported to co-occur but studies are not in agreement on whether psychotic symptoms precede depressive symptoms or vice versa (Aalten et al., 2003; Bassiony et al., 2002; Mizrahi et al., 2006; Wilkosz et al., 2007). Moreover, since psychotic behaviours have been associated with agitated behaviours (Lopez et al., 2003; Rapoport et al., 2001; Senanarong et al., 2004) and since the correlation between "psychosis" and "agitation" factor in the CFA model was

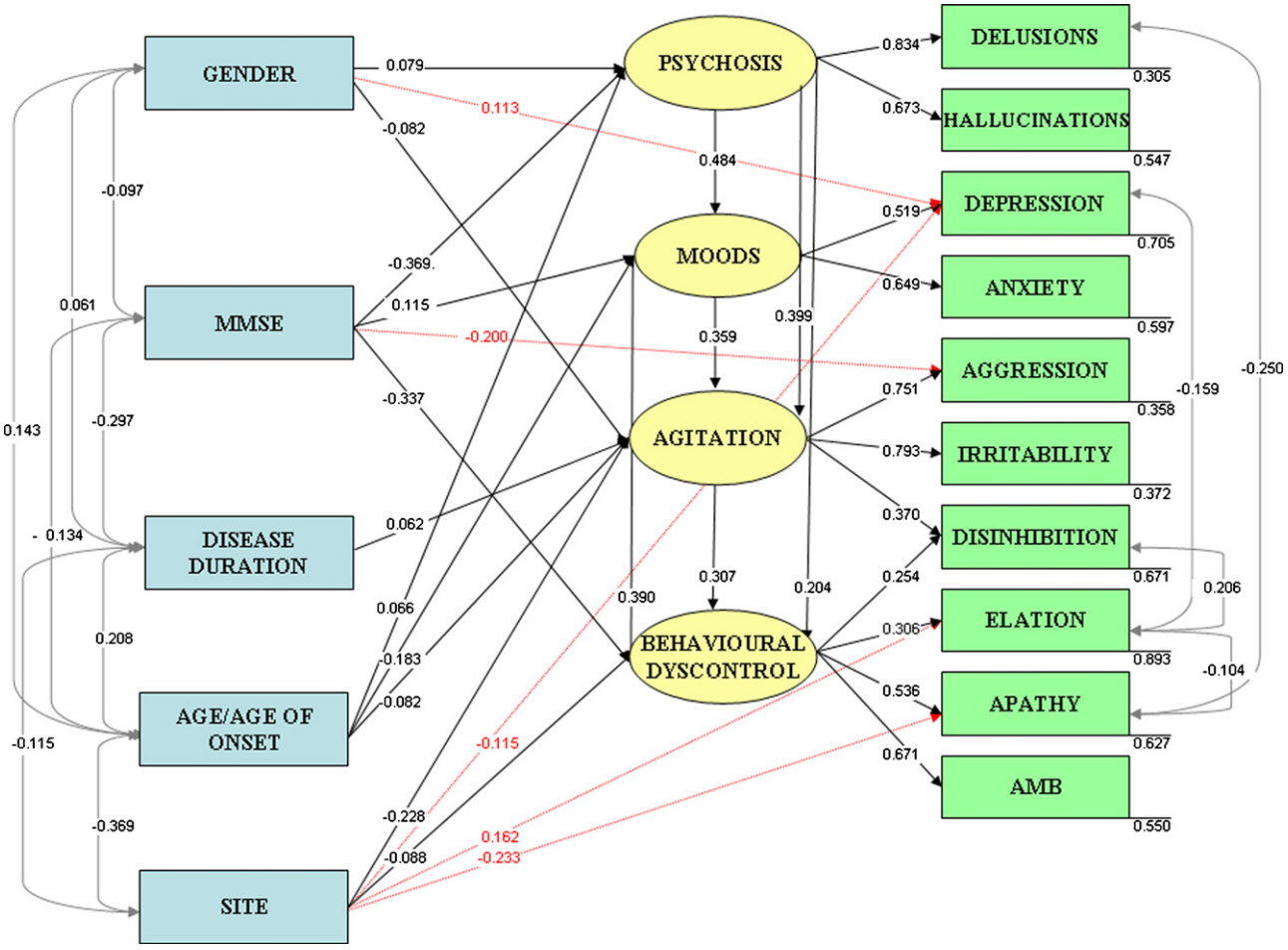

Fig. 1. Multiple Indicators Multiple Causes (MIMIC) model examining the impact of covariates on the four factors, and the impact of one factor on another. Red arrows indicate a direct effect between covariates and indicators after keeping the relevant factor constant. All paths drawn indicate significant associations ($p < 0.05$). All the correlations drawn between the covariates were significant at the $p < 0.0001$ level except for the correlation between gender and disease duration ($\rho = 0.011$).

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medium ($\rho = 0.558$) we hypothesised that "psychosis" factor could potentially predict some of the variability of "agitation" factor. Lastly, since the "behavioural dyscontrol" factor was highly associated with the rest of the factors we hypothesised that all factors could partially explain some of its variability. Positive associations could provide a starting point on testing these hypotheses using a longitudinal approach.

This model had a good fit ($\chi^2 = 67.367$, df = 41, $p = 0.0058$, RMSEA = 0.019 and CFI = 0.994) and we concluded that it was a very good approximation to the data. Overall, the addition of covariates did not affect the loadings of symptoms on factors. We also confirmed all of our hypotheses on the associations between the four factors in the presence of the covariates, except for the effect from "moods" factor to "psychosis" factor (Fig. 1). However, the significant increase in the χ^2 statistic between the CFA model and the MIMIC model highlighted a drop in the model fit (χ^2 difference test $p < 0.001$) and is indicative of the strong association between these covariates and the expression of behavioural sub-phenotypes. Table 2 shows the path coefficients for the effects of covariates on the four factors in the MIMIC model, as well as the path coefficients for inter-relationships of the factors.

Greater cognitive impairment was the most significant predictor of "psychosis" and "behavioural dyscontrol" factors but milder cognitive impairment was associated with the "moods" factor. Younger age/age of onset was a significant predictor of "moods" and "agitation" factors whereas older age/age of onset had a marginal association with "psychosis" factor. Only female gender was significantly associated with "psychosis" factor whereas male gender was only associated with the "agitation" factor. Long disease duration was a significant predictor of "agitation" factor. Lastly, site was significantly associated with the "agitation" and "behavioural dyscontrol" factors indicating higher "agitation" and "behavioural dyscontrol" factor mean scores for UK patients compared to Greek patients.

A direct association was observed between low MMSE scores and aggression. Even after controlling for the "agitation" factor, lower MMSE scores were still associated with aggression. A direct association was also observed between female gender and depression even though there was no

Table 2
MIMIC model results impact of MMSE, gender, disease duration, age/age of onset and site covariates on the "psychosis", "agitation", "moods" and "behavioural dyscontrol" factors and impact of individual factors on each other. Estimated direct effects of covariates on individual NPI items are noted on the bottom of the table.

Factor (% variance explained)	Covariates and significant factor effects on each factor	β	S.E.	p
Psychosis (16.8%)	MMSE	−0.369	0.030	<0.0001
	Gender	0.079	0.029	0.007
	Disease duration	0.040	0.030	0.183
	Age/age of onset	0.066	0.032	0.042
	Site	0.020	0.031	0.528
Agitation (44.3%)	MMSE[a]	0.061	0.038	0.112
	Gender	−0.122	0.029	<0.0001
	Disease duration	0.062	0.028	0.030
	Age/age of onset	−0.082	0.031	0.009
	Site	−0.228	0.030	<0.0001
	"Psychosis" factor	0.399	0.048	<0.0001
	"Moods" factor	0.359	0.048	<0.0001
Moods (22.6%)	MMSE	0.115	0.042	0.006
	Gender[b]	0.024	0.041	0.559
	Disease duration	0.048	0.036	0.182
	Age/age of onset	−0.183	0.037	<0.0001
	Site	0.011	0.044	0.802
	"Psychosis" factor	0.484	0.048	<0.0001
Behavioural Dyscontrol (77.5%)	MMSE	−0.337	0.038	<0.0001
	Gender	−0.022	0.031	0.474
	Disease duration	0.015	0.030	0.620
	Age/age of onset	−0.036	0.034	0.282
	Site[c]	−0.088	0.040	0.029
	"Psychosis" factor	0.204	0.064	0.002
	"Agitation" factor	0.307	0.057	<0.0001
	"Psychosis" factor	0.390	0.064	<0.0001

S.E. = Standard error.
[a] Low MMSE had a significant effect on aggression variable after controlling for "agitation" factor ($\beta = -0.200$, S.E. = 0.026, $p < 0.0001$).
[b] Female gender had a significant effect on depression variable after controlling for "moods" factor ($\beta = 0.113$, S.E. = 0.029, $p < 0.0001$).
[c] Site had a significant effect on apathy, elation and depression variables after controlling for the "behavioural dyscontrol" and "moods" factors ($\beta = -0.233$, S.E. = 0.026, $p < 0.0001$, $\beta = 0.162$, S.E. = 0.034, $p < 0.0001$ and $\beta = -0.115$, S.E. = 0.029, $p < 0.0001$, respectively).

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association between gender and the "moods" factor. Lastly, three direct associations were also observed between site and symptoms of apathy, elation and depression.

Overall, 17%, 44.3%, 22.6% and 77.5% of the variability of "psychosis", "agitation", "moods" and "behavioural dyscontrol" factors was explained respectively by this MIMIC model.

4. Conclusions

This study has extended previous studies on the factor structure of BPSD and proposed a systematic way to investigate the nature of behavioural sub-phenotypes in AD. To our knowledge, all the published studies classifying BPSD in AD have used an exploratory approach such as Principal Components Analysis (Aalten et al., 2003, 2007; Cook et al., 2003; Frisoni et al., 1999; Fuh et al., 2001; Gauthier et al., 2005; Harwood et al., 1998; Herrmann et al., 2005; Hollingworth et al., 2006; Hope et al., 1997; Lyketsos et al., 2001; Mirakhur et al., 2004; Moran et al., 2004; Spalletta et al., 2004; Tariot et al., 1995), with the exception of Borroni et al. (2006). Exploratory factor analysis techniques are essentially descriptive by nature and hypothesis testing is difficult, if not impossible. In contrast, CFA is a statistical methodology that takes a confirmatory (i.e. hypothesis-testing) approach to multivariate analysis and MIMIC modelling is an excellent approach to investigate the validity of a factor model in the presence of covariates.

Behavioural disturbances were evaluated using the 10 or 12 item NPI. The NPI is commonly used in research and clinical settings and its reliability and validity are well established. Although the majority of the aforementioned studies on BPSD have used have used the NPI, other neuropsychiatric inventories such as the Present Behavioural Examination scale and the BEHAVE-AD scales have been used, producing similar results (Hope et al., 1997; Harwood et al., 1998), suggesting that the this model reflects the underlying behavioural structure and is not specific to the NPI. The four factor structure of the NPI described here used the study by Hollingworth et al. (2006) as a starting point since half of the sample came from the same dataset. Some differences were however observed between the hypothesised and the reproduced model such as the positioning of apathy and disinhibition on their relevant factors. The models developed here have also indicated some unexplained correlations between NPI items, also known as error covariances which highlight that the variable associations are more complex than appeared in exploratory type analyses. Overall, with the exception of small differences the appearance of individual "psychosis", "moods" "agitation" and "behavioural dyscontrol" factors is replicated amongst BPSD studies although the factors generally explained only a moderate amount of the variability of each NPI item.

A MIMIC model was created to investigate whether and how cognitive impairment (MMSE), age/age of onset, disease duration and gender affected the predicted factor structure. Site was also added as a covariate to investigate measurement invariance and population heterogeneity since the datasets were from different research centres and ethnic groups. Various hypotheses on the effects a factor could have on another in the presence of these covariates were tested. This model was a very good approximation to the data but the significant drop in the χ^2-value from the CFA model and the significant associations between the covariates and the factors indicated that the covariates significantly affected the manifestation of the behavioural sub-phenotypes.

Although questions on the directions of effects between different factors can only be properly addressed with a longitudinal approach, a MIMIC model of a cross-sectional study may provide some clues to causality. We confirmed our hypotheses that the "psychosis" factor could partially explain some of the variability of the "agitation", "moods" and "behavioural dyscontrol" factor, that "moods" factor could partially explain some of the variability of "agitation" and "behavioural dyscontrol" factor and that the "agitation" factor could partially explain some of the variability of the "behavioural dyscontrol" factor.

When investigating the effect of covariates on the four factors, greater cognitive impairment was a significant predictor of the "psychosis", "moods" and "behavioural dyscontrol" factors; younger age/age of onset was a significant predictor of the "agitation" and "moods" factors whereas older age/age of onset was a marginally significant predictor of the "psychosis" factor; female gender was a significant predictor of the "psychosis" factor whereas male gender was a significant predictor of the "agitation" factor; long disease duration was a marginally significant predictor of the "agitation" factor only and lastly UK site was significantly associated with higher "agitation" and "behavioural disturbances" factor scores. We have also identified five significant direct associations between covariates and NPI items which highlight differences to the responses of the NPI items attributed to the covariate after controlling for the relevant factor (also known as Differential Item Functioning, DIF). The identification of such associations are very important when studying the effects of covariates on a factor model especially when, as in this case, some factors do not capture much of the variability of their indicators. For example, the "moods" factor explains only about ~30% of the variability of depression and the direct association between depression and female gender, after controlling for the lack of association between gender and "moods" factor, highlights an association of female gender with depression per se rather than with behavioural sub-phenotype. In addition the direct association between low MMSE scores and aggression highlights the higher correlation of severe cognitive impairment with aggression beyond the association of low MMSE with "agitation" factor. It is of interest that Craig et al. (2005) reported that as opposed to symptoms of aggression, symptoms of irritability were associated with MMSE scores over 20. Lastly, the negative direct associations of site with apathy and depression

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reflect significantly higher levels of apathy and depression in UK patients after controlling for the association of the "behavioural dyscontrol" with site and the lack of association between the "moods" factors with site. On the other hand, the positive direct association of site with elation is a consequence of the higher elation scores in Greek patients even though "behavioural dyscontrol" factor scores were higher in UK patients.

MIMIC models also allow for alternative models to be formed, where bi-directional effects between covariates and factors can be hypothesised. Such a hypothesis can be made for example for the direction of the relationship between cognitive impairment and psychotic symptoms. The association between cognitive impairment and psychosis in AD is not clear and although they are highly correlated it is difficult to establish which precedes which. Such analysis are however beyond the scope of the present study.

There are a number of limitations to the present study. A longitudinal approach such that employed by Aalten et al. (2005a,b) would be the ideal when investigating the direction of relationships between behavioural sub-phenotypes and this study has utilised data collected at a single time point. Follow up information would therefore support our hypotheses on the directionality of the relationships of the four factors and Structural Equation Modelling approaches are excellent tools in modelling time dependent data. In addition, we have used only the first 10 NPI items for the merged dataset as the Greek patients did not have data on sleep disturbances and appetite abnormalities.

In summary, the described MIMIC model in Fig. 1 underlines the complexity of the relationships of neuropsychiatric symptoms that affect AD patients and highlight the necessity of systematic statistical approaches such as MIMIC modelling to be used when investigating the nature of BPSD. We have shown that although different symptom factors exist, these are highly correlated and could potentially predict one another. Such observations underline the importance of testing the whole system of variables simultaneously and taking into consideration the fact that some factors could influence the onset of others. Models such as the one developed here highlight important associations between covariates and factors that may otherwise have been missed.

To our knowledge no other studies have applied statistical analysis tests when merging samples from different populations. Adding site as a covariate revealed population heterogeneity and such a step is important when analysing samples from different population groups. In addition to the studies investigating the existence of behavioural subphenotypes in AD, many studies have attempted to identify the genetic basis of BPSD (Borroni et al., 2004, 2006; Craig et al., 2004, 2006; Holmes et al., 1998, 2001; Sweet et al., 1998, 2001, 2005). The MIMIC model presented here can be tested statistically in a simultaneous analysis of the entire system of variables incorporating further genetic covariates. Such systematic analyses will help shed light into the nature of these common and disabling symptoms in AD.

Conflict of interest statement

There are no actual or potential conflicts of interest related to the work described in this paper, either by the authors or authors' institutions. Petroula Proitsi is an Alzheimer's Research Trust Post-Doctoral Fellow. DC Rubinsztein is a Wellcome Trust Senior Clinical Fellow.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2009.03.005.

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