

Grouping of behavioural and psychological symptoms of dementia[†]

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Objective: A wide range of behavioural and psychological symptoms (BPSD) are common in dementia, and it has been suggested that groups of correlated symptoms should be studied together. Here, we describe the groups of BPSD that have been identified in the literature and how they have been used to study associations, burden, treatment and underlying biology.

Methods: The literature database PubMed was searched for articles that identified clusters or factors of BPSD or used previously defined symptom groups.

Results: Sixty-two studies were included. Generally, the following symptom groups were suggested: affective symptoms, including depression and anxiety; psychosis, including delusions and hallucinations; hyperactivity, including irritability and aggression; and euphoria. Symptoms that did not show consistent results include apathy, eating disturbances, night-time behaviour disturbances, disinhibition and aberrant motor behaviour. Symptom groups differed in their associations, treatment and biology.

Conclusions: Studies investigating symptom groups show relatively consistent results. Studying symptom groups allows similar symptoms to be studied together, which might strengthen results and may point to differences in their aetiology and treatment. However, a large amount of the individual variability of the symptoms could not be explained by the factors, and authors should carefully address their research question and hypotheses to decide if symptoms should be studied in groups or individually. Clinicians need to consider each symptom in its own right and also to be aware of the interrelations between them when assessing patients and developing strategies for treatment. © 2013 The Authors. International Journal of Geriatric Psychiatry by John Wiley & Sons, Ltd.

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Introduction

A wide range of behavioural and psychological symptoms are common in dementia, including dysphoria, anxiety, apathy, psychosis, aberrant motor behaviour, irritability, aggression, eating disturbance and sleep disorders. These symptoms confer a large proportion of the social burden of dementia and are important targets for intervention. Traditionally, authors have focused on a single symptom, such as depression. However, since the introduction of the term 'Behavioural and Psychological Symptoms of Dementia' (BPSD) by the International

Psychiatric Association in 1996 (Finkel *et al.*, 1996) and the development of instruments measuring several BPSD such as the Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) and Behavioral Pathology in Alzheimer's Disease Scale (Reisberg *et al.*, 1987), it has become more common to study a wider range of symptoms. Some report on each of the symptoms individually, whereas others use the total score of a BPSD-specific instrument. Certain symptoms, such as depression and anxiety, are frequently seen together and may have a similar aetiology. Therefore, it has been suggested that groups of correlated symptoms should be studied together.

A consensus review paper of the European Alzheimer disease consortium concluded that there is some clinical evidence for groups of BPSD and that it might be a more effective strategy to examine interventions for groups of symptoms rather than individual symptoms (Robert *et al.*, 2005). The US Food Drug Association has considered BPSD too broad a target for treatment as it refers to multiple clinical entities and proposes to 'identify and define unique psychiatric/behavioural syndromes' (FDA, 2000). This issue is important not only for purposes of taxonomy and research but also for everyday clinical practice, in terms of communication between clinicians, patients and families, and in terms of setting clear goals for therapeutic efforts.

Symptom groups

may point to a common neurobiological pathogenesis, or may react to the same treatment. For example, pharmacological studies have shown that treatments may have a consistent effect on behavioural problems in dementia when studying behavioural subsyndromes, but not when studying individual symptoms. Data reduction, through the reduction of a number of symptoms into subsyndromes, leads to greater possibility of finding associations. (Aalten *et al.*, 2003)

Symptom groups can be identified with different statistical techniques. They explore the patterns of correlated variables (e.g. BPSD) and group them into 'factors' or 'clusters'. In cluster analysis and latent class analysis, patients are grouped on the basis of their symptom profile, leading to non-overlapping clusters of patients. In contrast, in factor analysis and principal component analysis, symptoms rather than patients are grouped, and an individual patient may have more than one factor of symptoms, whereas an individual symptom may appear in more than one factor. In addition, clinical judgement based on the occurrence of symptoms in the clinic and hypotheses regarding their aetiology can be used to group symptoms, as well as studies of the correlation between individual symptoms.

We do not readily know which is the most valid method for grouping symptoms (that is, which symptoms should be grouped together as well as how many symptom groups). Especially if clinical judgement is used, this may be biased by implicit or explicit assumptions. On the other hand, a purely statistical means of factor selection may not be clinically relevant. Here, we describe the groups of BPSD that have been identified in the literature and how they have been cited.

To explore the suggestion that symptom groups differ in aetiology and treatment, differences between symptom groups in their associations, burden, treatment and underlying biology are reported.

Methods

Studies identifying BPSD groups

The literature database PubMed was searched for articles that identified clusters or factors of BPSD. The following search terms were used: text terms for BPSD, MeSH term 'cluster analysis', text terms 'cluster' or 'factor' and MeSH term 'dementia' (Additional File 1). References from the included studies were also investigated as well as references from relevant literature reviews.

Studies that identified BPSD symptom groups in people with dementia using factor analysis, cluster analysis, principal component analysis or latent class analysis were included. Non-English papers were excluded. Study characteristics were extracted, including statistical methods used, BPSD instrument, setting, number of participants, country, mean age, type of dementia, mean Mini Mental State Examination (MMSE) and if the study was cross-sectional or longitudinal.

Symptom names and definitions as used by the NPI were used where possible: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour disturbances and appetite and eating disturbances. Symptom groups with an eigenvalue greater than 1 were reported. Symptoms were included in a symptom group if their absolute factor loading was 0.4 or above and symptoms could load on more than one factor. Symptom groups that were identified were named on the basis of the symptoms within the factor, the factor loading of these symptoms and the symptom group name provided by the author. Results from studies using the NPI and studies using other instruments were reported separately.

Studies citing papers that identified NPI symptom groups

The literature database Scopus was searched for studies citing the included papers that identified NPI symptom groups. Studies that used NPI symptom groups previously defined in the literature to further study the associations or impact of the symptom groups were included. We excluded studies that did not provide details on how the symptom groups were defined or which citation they were based on.

The main results that were reported by the included studies on the associations, burden, treatment and biology of NPI symptom groups were extracted.

Results

Identification of symptom groups

The search resulted in 157 studies, of which 31 reported on the identification of symptom groups (Additional File 2). Cross-referencing resulted in an additional 31 studies. Therefore, in total, 62 studies were included. Of these, 39 used the NPI to measure BPSD. The study characteristics, the symptom groups that were found and the total variance explained is summarised in Additional File 3. Principal component analysis was used by 29 studies (of which $n = 19$ used the NPI), factor analysis by $n = 25$ (NPI $n = 14$), latent class analysis by $n = 4$ (NPI $n = 3$) and cluster analysis by $n = 8$ (NPI $n = 7$). The studies have recruited participants from a wide range of settings, countries and age groups and with varying dementia severity.

Neuropsychiatric inventory. Generally, the studies using the NPI suggest the following symptom groups:

- Affective symptoms: dysphoria and anxiety, sometimes also including apathy, hallucination, or sleeping problems
- Psychosis: delusions and hallucinations, sometimes also including sleeping problems or aberrant motor behaviour
- Hyperactivity: irritability and aggression, sometimes also including aberrant motor behaviour, disinhibition, anxiety or euphoria
- Euphoria, sometimes also including disinhibition

Symptoms that did not show consistent results include apathy, eating disturbances, night-time behaviour disturbances, disinhibition and aberrant motor behaviour.

The number of times individual symptoms were included in these symptom groups by 29 studies using the NPI has been summarised in Figure 1. Figure 1 includes only those studies that used factor analysis (and therefore group symptoms). Those using cluster analyses or latent class analysis (and therefore group

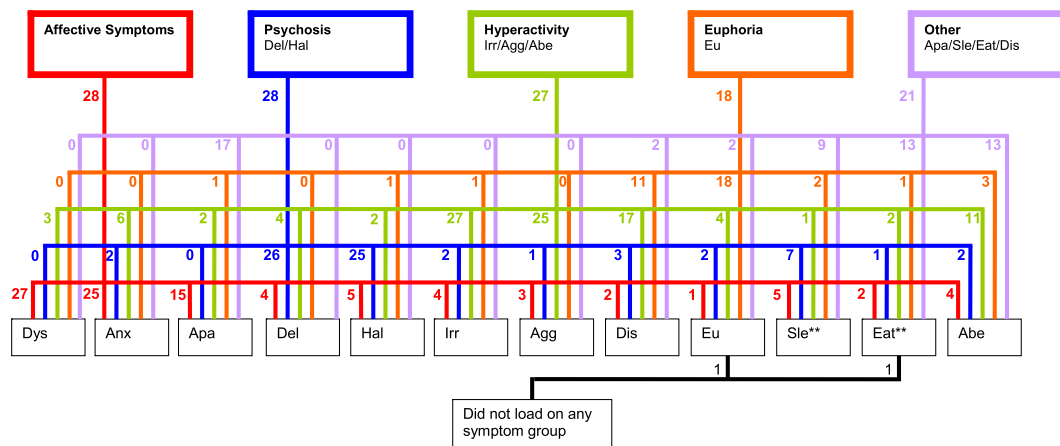


Figure 1 Number of times individual symptoms have been included in the symptoms groups affective symptoms (red), psychosis (blue), hyperactivity (green), euphoria (orange) or other (purple), as identified by $n = 29^*$ studies using the Neuropsychiatric Inventory. For example, a factor of affective symptoms (red) was identified by $n = 28$ studies; depressive symptoms were included in this factor by all but one of the studies, anxiety by $n = 25$ and apathy by $n = 15$. Other symptoms such as hallucinations, irritability, sleep problems and wandering were included in this symptom group by some. Although anxiety was most often included in the affective symptoms group, six studies found it was associated with symptoms of hyperactivity (green). Full details of the study design and results of each of the studies are included in Additional File 3. Factor loadings of 0.40 or above are included. Symptoms can load on more than one factor. Symptom groups are defined on the basis of those factors most often reported by the studies. When factors include symptoms from more than one of the defined groups, the factor is mapped to the group with which it shares the highest number of symptoms and/or symptoms with the highest factor loading. When two or more 'other' factors were identified, both are included in the 'other' group. *Studies using cluster analysis or latent class analysis are not included. For studies reporting both explanatory factor analysis and confirmatory factor analysis, only confirmatory factor analysis is included. Zuidema *et al.* (2007) report on three subgroups that are included separately. Vilalta-Franch *et al.* (2010) reports on the same sample as Garre-Olmo *et al.* (2010a, 2010b) and is excluded from the figure. The sample included (Dechamps *et al.*, 2008) overlaps with Prado-Jean *et al.* 2010 and is excluded from the figure. Germain *et al.* 2009, Petrovic *et al.* 2007 and Aalten *et al.* 2007 all report on European Alzheimer's Disease Consortium (EADC) data; only Aalten *et al.* is included in the figure. When a study reports on several different samples (including Truzzi *et al.* and Zuidema *et al.*, 2007), results are reported separately for each sample. **Included in NPI-12 only. Del, delusions; Hal, hallucinations; Agg, agitation/aggression; Dys, dysphoria; Anx, anxiety; Eu, euphoria; Apa, apathy; Dis, disinhibition; Irr, irritability/lability; Abe, aberrant motor behaviour; Sle, night-time behaviour disturbances; Eat, appetite and eating disturbances.

participants) were excluded from Figure 1, but they were included in the tables (included as additional files and referred to in the following text). When several studies reported on the same sample, only one study was included in Figure 1. The total variance that was explained by the symptom groups in these studies ranged from 41% to 76%. In 13 of 20 studies ($n = 9$ did not report the total variance or used confirmatory factor analysis), the symptom groups explained less than 60% of the variance. Affective symptoms and aggression were sometimes grouped with other factors (Garre-Olmo *et al.*, 2010b; Selbaek and Engedal, 2012), and apathy and aberrant motor behaviour were found to be less stable and related to different symptoms over time (Garre-Olmo *et al.*, 2010b; Vilalta-Franch *et al.*, 2010).

The four longitudinal studies that reported factor solutions at different time points generally showed results were relatively stable over time (Colombo *et al.*, 2007; Garre-Olmo *et al.*, 2010b; Vilalta-Franch *et al.*, 2010; Selbaek and Engedal, 2012). Eight studies that used the NPI and cluster analysis or latent class analysis reported similar groups to those reported by studies using factor analysis or principal component analysis, including affective symptoms ($n = 8$), psychosis ($n = 5$) and hyperactivity ($n = 2$), in addition to a group of participants with few symptoms ($n = 5$) or who are highly symptomatic ($n = 1$).

Other instruments. The studies that use instruments other than the NPI, such as Behavioral Pathology in Alzheimer's Disease Scale (Reisberg *et al.*, 1987), Neurobehavioral Rating Scale (Sultzer *et al.*, 1992) and Behaviour Rating Scale for Dementia (Overall and Gorham, 1962), found results similar to those from studies using the NPI. The total variance reported by these studies ranged from 39% to 72%, with 9 of 13 studies reporting a variance below 60%. When measured, inappropriate behaviours such as inappropriate urinating, faecal smearing and stripping formed a separate group (Lam *et al.*, 2006a; Lovheim *et al.*, 2008) or were grouped with irritability (Youn *et al.*, 2008).

Differences by cognitive function. No clear differences were seen between studies of populations with different cognitive function. Zuidema *et al.* (2007) found that symptom groups were relatively stable across dementia stages. Previous results from our group found that the factor structure in those without dementia is largely consistent across mild cognitive impairment subtypes and those with mild and moderate cognitive impairment and is similar although with weaker

associations to that seen in the population with dementia (Savva *et al.*, 2009; van der Linde *et al.*, 2010).

How studies identifying NPI symptom groups have been cited

Some of the studies identifying NPI symptom groups (Lyketsos *et al.*, 2001; Aalten *et al.*, 2003; Mirakhor *et al.*, 2004; Borroni *et al.*, 2006; Hollingworth *et al.*, 2006; Matsui *et al.*, 2006; Aalten *et al.*, 2007; Tun *et al.*, 2007; Zuidema *et al.*, 2007; Spalletta *et al.*, 2010; Proitsi *et al.*, 2011) have been cited by other papers in which the associations or impact of the symptom groups were analysed further. This is shown in Additional File 4. The symptom groups defined by Aalten *et al.* have been cited most frequently (Aalten *et al.*, 2003). However, most studies do not use symptom groups but study individual symptoms or the total score on the NPI. The symptom groups that were derived by the studies that have subsequently been cited in other relevant papers (these studies have been underlined in Additional File 3) are similar to symptom groups that were identified by the other studies included in Additional File 3.

Differences between NPI symptom groups in associations, burden, treatment and biology

In total, 18 of the studies that identified NPI symptom groups and 17 of the studies that cite previously defined NPI symptom groups report on the associations and outcomes of symptom groups. These 34 studies reported on the associations ($n = 15$), course ($n = 2$) or burden of symptoms ($n = 6$), the most effective treatment ($n = 6$) or the underlying biology of symptoms ($n = 5$) (Additional File 5). Studies reported associations with the factor score, the mean instrument score within each symptom group or with a dichotomous or categorical variable of the presence of one or more of the symptoms within a symptom group.

Associations. Several studies reported an association between symptom groups and cognitive function. There were some differences between symptom groups. For example, Proitsi *et al.* found that affective symptoms were associated with milder cognitive impairment, whereas psychosis was associated with greater cognitive impairment and the hyperactivity cluster was not associated after adjustment for correlations between symptom groups (Proitsi *et al.*, 2011). Most other studies confirm the association between psychosis and more severe cognitive impairment

(Frisoni *et al.*, 1999a; Hollingworth *et al.*, 2006; Spalletta *et al.*, 2010; Tsai *et al.*, 2010; Koppel *et al.*, 2012), but the results for the association between affective symptoms and cognitive function were mixed, with some reporting no association (Frisoni *et al.*, 1999a; Lam *et al.*, 2006b; Spalletta *et al.*, 2010; Tsai *et al.*, 2010; Palmer *et al.*, 2011) and others reporting an association with greater cognitive impairment (Hollingworth *et al.*, 2006; Koppel *et al.*, 2012).

Psychosis has been associated with older age at dementia onset (Frisoni *et al.*, 1999b; Proitsi *et al.*, 2011), whereas affective symptoms have been associated with younger age at dementia onset (Hollingworth *et al.*, 2006; Proitsi *et al.*, 2011). Hyperactivity symptoms have been associated with functional disability and lower premorbid agreeableness, whereas these associations are less strong or not seen for the other symptom groups (Archer *et al.*, 2007; Peters *et al.*, 2008). Studies investigating the course of symptom groups showed that hyperactivity symptoms increase over time, whereas affective and psychotic symptoms remained stable (Garre-Olmo *et al.*, 2010a; Gonfrier *et al.*, 2012).

Burden. All symptom groups have been associated with caregiver distress or quality of life, although only a limited number of studies have investigated this association (Mourik *et al.*, 2004; Tun *et al.*, 2007; Tun *et al.*, 2008; Germain *et al.*, 2009; Tatsumi *et al.*, 2009; Rocca *et al.*, 2010). Results were generally similar across symptom groups, although some did not report an association for affective symptoms (Germain *et al.*, 2009), psychotic symptoms (Tun *et al.*, 2008), euphoria (Mourik *et al.*, 2004; Tatsumi *et al.*, 2009), apathy (Mourik *et al.*, 2004) or sleep problems (Germain *et al.*, 2009).

Treatment. Treatment effects differed by symptom groups. For example, donepezil was found to improve affective symptoms (Cummings *et al.*, 2006) and psychotic symptoms (Gauthier *et al.*, 2002; Cummings *et al.*, 2006), whereas mixed results were found for hyperactivity symptoms (Gauthier *et al.*, 2002; Cummings *et al.*, 2006), and no significant improvement was seen for the elation group (Gauthier *et al.*, 2002; Cummings *et al.*, 2006). Galantamine improved psychotic symptoms but not affective symptoms (Herrmann *et al.*, 2005).

Underlying biology. A limited number of studies studying a range of biological association found some differences between symptom groups, including genetic associations for psychotic and hyperactivity symptoms but not for affective symptoms (Borrioni

et al., 2006), inconsistent associations with apolipoprotein E (D'Onofrio *et al.*, 2011; Chen *et al.*, 2012) and differences in the associations with serotonin and dopamine receptor polymorphisms (Proitsi and Powell, 2012).

Discussion

Summary of results

Generally, studies identified and used the following symptom groups: affective symptoms, psychosis, hyperactivity (sometimes named agitation or psychomotor symptoms) and euphoria. There were small differences in factor solutions between studies that are likely to be caused by the large differences in population characteristics and study design, including setting, population age, dementia severity and dementia type. The most problematic symptom is apathy, which was observed to be loading on any factor. There is some overlap between apathy and dysphoria or depression, although both can occur without the other (Starkstein *et al.*, 2005). This was reflected by our results; in 9 studies, apathy was included in the affective factor, whereas it occurred independently or was associated with other symptoms such as sleep problems and/or appetite changes in 14 studies. The inconsistent loading of apathy does pose a problem as we know that apathy is an important symptom in terms of predicting poor outcomes for people with dementia (Landes *et al.*, 2001; Starkstein *et al.*, 2006; Benoit *et al.*, 2008), so understanding more about it is important both scientifically and clinically.

Most studies used the NPI, the most commonly used instrument to measure BPSD (Cummings *et al.*, 1994; van der Linde *et al.*, 2013). However, studies using other instruments found similar results, suggesting these symptom groups are not specific to the NPI. The results of the studies included in this review confirm that there are differences between symptom groups in their associations, treatment and biology, although because of the wide range of objectives and study designs that were included, we were not able to draw firm conclusions.

It might also be asked if the statistically derived symptom groups are meaningful in everyday terms. This has not been examined directly in this paper, but it does seem reasonable on the grounds of clinical experience that depression, psychosis and agitated/overactive/aggressive behaviour are consistent problems for carers across the whole range of dementia.

Strengths and limitations

We have provided a detailed overview of the symptom groups identified in the literature, including details on the population characteristics and study design of the included studies and the total variance that was explained. In addition, we have reported the use of these symptom groups by other authors. Studies often did not list 'cluster analysis' as a key word or did not describe the symptom groups in the abstract, and relatively many studies were found through searching the reference lists of included papers. In addition, there is no MeSH search term for BPSD. One author (RvdL) undertook data selection and extraction.

Recommendations for research and clinical practice

Behavioural and psychological symptoms have been studied in different ways, each with advantages and disadvantages. A single symptom can be studied individually, for example, depression in older adults, allowing a detailed study of the symptom and an in-depth assessment with a symptom specific instrument. However, this method does not take into account the correlations with other BPSD. Others have studied a range of individual symptoms using an instrument measuring several BPSD such as the NPI, adjusting each of the symptoms for the other BPSD. Although this allows for correlations between symptoms, symptoms are heterogeneous, and testing for each of 12 symptoms might obscure associations and introduce error. A third way of studying BPSD is the use of the total score of an instrument measuring a range of BPSD. This might not take into account the different nature of individual symptoms.

In this review, we have shown that studies investigating symptom groups show relatively consistent results and suggest symptom groups differ in their associations, treatment and underlying biology. This method allows similar symptoms to be studied together, which might strengthen results and may point to differences in their aetiology and treatment. However, a large amount of the individual variability of the symptoms could not be explained by the factors. Taking into account the advantages and disadvantages of each of these methods, authors should carefully address their research question and hypotheses to decide if symptoms should be studied in groups or individually.

In similar fashion, clinicians need to consider each symptom in its own right and also to be aware of the interrelations between them when assessing patients and developing strategies for treatment. Using the symptom

groups in future studies and reviews to study the prognosis, burden, treatment and neurobiology and genetic associations of BPSD is recommended to further test the hypothesis that these symptom groups have a common aetiology and disease course and may react to the same treatment.

Conflict of interest

None declared.

Key points

- The following symptom groups were identified and used in the literature: affective symptoms, psychosis, hyperactivity and euphoria.
- Studying symptom groups allows similar symptoms to be studied together, which might strengthen results and may point to differences in their aetiology and treatment. However, a large amount of the individual variability of the symptoms could not be explained by the factors.
- Authors should carefully address their research question and hypotheses to decide if symptoms should be studied in groups or individually. In similar fashion, clinicians need to consider each symptom in its own right and also to be aware of the interrelations between them when assessing patients and developing strategies for treatment.

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Supporting information

Additional supporting information may be found in the online version of this article:

Additional File 1. Search terms

Additional File 2. Overview search results

Additional File 3. BPSD symptom groups

Additional Table 4. How studies identifying Neuropsychiatric Inventory groups have been cited in the literature

Additional File 5. Associations, course, burden, treatment and biology of NPI symptom groups