



Behavioral and psychological symptoms of dementia

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Behavioral and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, represent a heterogeneous group of non-cognitive symptoms and behaviors occurring in subjects with dementia. BPSD constitute a major component of the dementia syndrome irrespective of its subtype. They are as clinically relevant as cognitive symptoms as they strongly correlate with the degree of functional and cognitive impairment. BPSD include agitation, aberrant motor behavior, anxiety, elation, irritability, depression, apathy, disinhibition, delusions, hallucinations, and sleep or appetite changes. It is estimated that BPSD affect up to 90% of all dementia subjects over the course of their illness, and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, misuse of medication, and increased health care costs. Although these symptoms can be present individually it is more common that various psychopathological features co-occur simultaneously in the same patient. Thus, categorization of BPSD in clusters taking into account their natural course, prognosis, and treatment response may be useful in the clinical practice. The pathogenesis of BPSD has not been clearly delineated but it is probably the result of a complex interplay of psychological, social, and biological factors. Recent studies have emphasized the role of neurochemical, neuropathological, and genetic factors underlying the clinical manifestations of BPSD. A high degree of clinical expertise is crucial to appropriately recognize and manage the neuropsychiatric symptoms in a patient with dementia. Combination of non-pharmacological and careful use of pharmacological interventions is the recommended therapeutic for managing BPSD. Given the modest efficacy of current strategies, there is an urgent need to identify novel pharmacological targets and develop new non-pharmacological approaches to improve the adverse outcomes associated with BPSD.

Keywords: behavioral and psychological symptoms, dementia, neuropsychiatric symptoms, Alzheimer's disease

INTRODUCTION

During the natural course of dementia a heterogeneous group of clinical phenomena is subjectively experienced by the patient and/or observable by an examiner (e.g., caregiver, physician) consisting in disturbed emotions, mood, perception, thought, motor activity, and altered personality traits. These “neuropsychiatric symptoms,” according to the terminology most used in the United States, or “behavioral and psychological symptoms of dementia” (BPSD), as designated by the International Psychogeriatrics Association (Finkel et al., 1996), are very common and associated with high levels of distress both in dementia sufferers and their caregivers, as well as with adverse outcomes and increased use of health care resources. Thus, in addition to cognitive deterioration, BPSD are a relevant and meaningful clinical target for intervention (Katona et al., 2007).

BPSD: CONCEPTUAL OVERVIEW

BPSD IN THE CURRENT CLASSIFICATION SYSTEMS

Despite being almost universally present during the course of dementia, BPSD have not been included in the defining criteria of dementia in the current classification systems. The core features of dementia according to DSM-IV-TR and ICD-10 consist

of gradual onset of multiple cognitive deficits (involving memory and at least one additional cognitive domain) not occurring exclusively during delirium and representing a decline from a previous level of functioning (American Psychiatric Association, 1994). In DSM-IV-TR the presence or absence of a clinically significant behavioral disturbance can be coded, but no guidance is provided about the diagnostic criteria of these symptoms. It is also possible to code dementia (e.g., Alzheimer disease, AD) in axis III and specific mental disorders (e.g., mood or psychotic disorder) in axis I with the advantage of better characterizing prominent clinical features related to dementia (American Psychiatric Association, 1994).

PSYCHOPATHOLOGICAL FEATURES

Neuropsychiatric symptoms in subjects with dementia are heterogeneous and largely unpredictable, affecting the emotional experience, thought content, perception, and motor function. While some symptoms can be more often recognized in a specific pathological sub-type, the clinical presentation has a wide variation within each sub-type and even within each dementia individual. The first step to better understand the psychiatric manifestations of dementia is to appropriately recognize and describe

the psychopathology and accurately distinguish between similar symptoms (e.g., depression vs. apathy). This can be challenging considering the overlap between symptoms and the lack of proper definitions and consensus criteria for their diagnosis. Secondly, it is useful to evaluate whether specific symptoms occur in association and to group them in syndromes with common clinical evolution, neurobiology, and management.

Disturbances in emotional experience

As the symptoms of depression are frequently masked by dementia, the patient rarely is able to express the typical pathological feelings of sadness, unhappiness, and preoccupation with depressing topics, hopeless (strongly associated with suicidal ideation) and loss of self-esteem (Prado-Jean et al., 2010). Instead, the prominent symptoms can be anhedonia (lost of interest in previous pleasurable stimuli), expression of somatic concerns and anxiety, a subjective unpleasant experience of fear manifested as apprehension, tension, panic, or worry associated with autonomic activation and observable physical and motor manifestations of tension. In the context of dementia, apathy has been defined as a disorder of motivation with additional loss or diminished goal-directed behaviors, cognitive activities and emotions (Robert et al., 2009). Apathy may be mistaken for depression because both symptoms can manifest themselves as diminished interest, slowing and lack of energy (Mulin et al., 2011). Although lack of motivation occurs both in apathy and depression, apathy denotes a lack of motivation without dysphoria. Elated mood, ranging from hypomania to severe mania, refers to a sustained and exaggerated feeling of well-being, cheerfulness, euphoria that is out of proportion to the circumstances often associated with a heightened emotional tone or emotional reactivity. Both depression and elated mood are commonly associated with irritability, a pervasive feeling of unease in response to a sense of threat with enhanced readiness to hostile attitudes or actions, which can be aggravated by hunger, sleepiness, and pain. Affective (or mood) lability is characterized by rapid emotional shifts, within seconds or minutes.

Delusions and abnormal thought content

Delusional ideas (false beliefs strongly held, enduring, and irrefutable) can vary widely in respect to complexity, systematization, conviction, and the extent to which patients take action in response to them. The delusions are typically less complex and organized than those observed in non-demented psychotic patients and the usual content of delusional thoughts involves suspiciousness, abandonment, and misidentification (Jeste et al., 2006). Common examples include the conviction that: people are coming into the home and hiding/stealing objects; the place in which one is residing is not one's home; conviction that spouse is an impostor (Capgras delusion); accusation of a conspiracy to abandon or institutionalize; conviction that spouse is unfaithful; believes that other persons have acted maliciously; or with discriminatory intent (Tariot et al., 1995). When associated with severe depression, delusional thoughts can involve guilt, worthless, reference, and persecution.

PERCEPTUAL DISTURBANCES

Perceptual disturbances in dementia can occur in every sensorial modality. In some instances, it is somewhat difficult to ascertain

whether the perceptual disturbance is an illusion or whether the patient is having a perception in the absence of sensory stimuli (hallucination). Visual hallucinations are particularly common in subjects with dementia with Lewy bodies (DLB). They are recurrent, and typically consist of well formed images of animals or persons that the patient describes in detail (McKeith et al., 2005).

DISTURBANCES IN MOTOR FUNCTION

Unlike the prior psychopathological domains, disturbances in motor function can be directly observed and consist in reduced or increased motor activity, not necessarily associated with specific motor abnormalities. In *motor retardation* the patient presents with slowed movements and speech, reduced body tone, and decreased number of spontaneous body movements, whereas *motor hyperactivity* is characterized by an increased energy level with more frequent movements and/or rapid speech.

Agitation has been defined as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the agitated individual" (Cohen-Mansfield et al., 2010). This term is used interchangeably with aberrant motor behavior and encompasses a range of activities such as wandering away from home; repetitive, purposeless behaviors; social inappropriate activities including those associated with disinhibition (tendency to disregard social and cultural norms and not restrain inner feelings, such as sexual drives). According to Cohen-Mansfield (1999) four distinct categories of agitation are: (1) physically non-aggressive behavior; (2) verbally non-aggressive behavior; (3) physically aggressive behavior; and (4) verbally aggressive behavior.

CIRCADIAN RHYTHMS

Sleep pattern changes may occur as a consequence of normal aging, but are particularly prevalent in individuals with dementia. These include hypersomnia, insomnia, sleep-wake cycle reversal, fragmented sleep, and rapid eye movement sleep behavior disorder. Patients with dementia often show daytime napping and nighttime awakenings associated with poor quality of sleep (Rongve et al., 2010). Several factors, e.g., pain, need to urinate during the night, medications (diuretics), as well as stimulants such as coffee and bronchodilators, may contribute to this problem.

APPETITE AND EATING BEHAVIOR

Appetite changes can be quantitative (anorexia or hyperphagia) or qualitative (preference for particular foods associated or not to changes in taste). The preference for sweets is particularly frequent in fronto-temporal dementia. Most dementia patients lose weight which can be due to hypermetabolism and inflammatory processes, in relation with hormonal disturbances.

BPSD ASSESSMENT

The assessment of neuropsychiatric symptoms requires a thorough examination to collect specific and detailed information about the clinical history, patient's subjective experiences, and objective behavior. Information from a reliable family member or caregiver is essential to obtain adequate characterization of neuropsychiatric disturbances from the patient's own ecological context as many abnormal symptoms cannot be elicited during the clinical interview. When determining whether the disturbances require medical

attention it is useful to promote early interventions instead of a crisis-based or reactionary approach.

INTERVIEW WITH THE PATIENT

Although subjects with dementia may be handicapped in their communication and social skills, it is essential to have an individual assessment with them. Whenever possible, it is desirable that patients are encouraged to express their own concerns in answer to open questions before proceeding to a more systematic approach to specific symptoms. Patient's free descriptions are least prone to be influenced by the interviewer and/or caregiver and can provide crucial information about emotional states underlying behaviors.

CAREGIVER INTERVIEW

The interview with caregivers is an opportunity to characterize the psychopathological features and to recognize which BPSD are of greatest concern to them as these may not necessarily coincide with the patient's own complaints or with the clinician's priorities.

Understanding the sources of these discrepancies is important to determine the usefulness and limitations of the information obtained from both patients and caregivers as caregiver's emotional state can influence assessment ratings (Logsdon et al., 1999; Snow et al., 2005; Karlawish et al., 2008). In some parts of the assessment, it is important to observe how caregivers interact with the patient and how symptoms are manifested in such interactions. Behavioral symptoms, particularly apathy, have a significant impact in the patient-caregiver relationship deterioration (de Vugt et al., 2003) and subjects with dementia are likely to be affected by dysfunctional interactions with their caregivers (de Vugt et al., 2004; Sink et al., 2006). Caregiver's characteristics, such as younger age, less education, depressive symptoms, and more hours per week providing care assistance, appear to contribute to the presence of or reported higher rates of BPSD (Sink et al., 2006). However, more research is needed to clarify how the patient-caregiver interpersonal interactions contribute to the presence of certain neuropsychiatric symptoms.

STANDARDIZED CLINICAL ASSESSMENT

Several validated instruments have been developed to quantify BPSD based on data collected from clinical assessment of dementia patients and caregivers' interviews with some scales assessing a wide range of neuropsychiatric symptoms and others focusing on specific symptoms (e.g., aggression and agitation). Self-administered questionnaires are also available for caregivers.

The first behavior rating scale for AD was the *BEHAVE-AD* (Reisberg et al., 1987), evaluating the presence and severity of 25 behavioral symptoms in 7 symptomatic categories (paranoid and delusional ideation, hallucination, activity disturbances, aggressiveness, sleep disturbances, affective symptoms, and anxieties and phobias), and providing a global rating of caregiver burden. Currently, one of the most extensively used instruments to assess BPSD is the *Neuropsychiatric Inventory* (NPI) whose validity and reliability has been well established in several languages (Cummings, 1997). It consists of a semi-structured interview retrospectively assessing 12 symptoms based on the caregiver information: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night

time behavior disturbances, and eating behavior abnormalities. Important factors to take into account when selecting an instrument include the purpose of the assessment (e.g., comprehensive vs. specific symptom evaluation) and the setting (e.g. busy clinical practice vs. research). When possible, it is advisable to obtain information from different caregivers to cover behavior in different settings, and thus providing an overall picture of patient's functioning. Disagreements among informants should be regarded as a valuable cue to identify situational factors implicated in the genesis of symptoms. It is unlikely that new rating scales will completely solve the problems that are inherent in the assessment of BPSD. Yet, future challenges lie in the improvement of the construction and the use of the scales with an increasing need for more standardized assessment of BPSD and for evaluation of their treatment.

CLINICAL RELEVANCE OF BPSD

PREVALENCE AND SEVERITY OF INDIVIDUAL SYMPTOMS

There is an overall agreement that BPSD are very common regardless of the type of dementia and are present in virtually all patients during the course of their disease. Even in the early stages of cognitive impairment, neuropsychiatric symptoms are frequent with estimated rates of 35–85% in subjects with mild cognitive impairment (MCI; Monastero et al., 2009).

The reported frequency of BPSD largely depends on the type of sample and setting considered. In community-dwelling subjects with dementia, neuropsychiatric symptoms are generally less frequent (56–98%) and severe than in patients recruited in hospital or long-term care facilities (91–96%). When looking at individual symptoms in dementia patients, the most prevalent BPSD are apathy, depression, irritability, agitation and anxiety, while the rarest are euphoria, hallucinations, and disinhibition. The most clinically significant symptoms are depression, apathy, and anxiety. Importantly, 50% of patients have at least four neuropsychiatric symptoms simultaneously (Frisoni et al., 1999).

THE BURDEN OF BPSD

BPSD are a source of significant distress and poor quality of life (QoL) to both dementia patients and their caregivers (Ryu et al., 2011). In AD patients, depressive symptoms are associated with worse self-reported QoL scores (Karttunen et al., 2011) whereas mood and psychotic symptoms predict changes in the QoL 2 years later (Tatsumi et al., 2009). Moreover, increased number of BPSD correlates negatively with survival rates over a 3-year period (Tun et al., 2007) whereas presence of psychosis in AD has been found to be associated with increased mortality and acceleration of cognitive decline (Emanuel et al., 2011; Russ et al., 2011).

BPSD also have a profound physical and psychological impact on both formal and informal caregivers. A considerable part of caregivers' time and distress relate directly to the manifestation of BPSD (Ballard et al., 2000a), which is a major reason for earlier institutionalization of patients (Chan et al., 2003). Nursing home placement determines a significant increase in the overall cost of dementia care in addition to other direct and indirect costs associated with BPSD (Beeri et al., 2002; Herrmann et al., 2006). Psychotic symptoms (e.g., delusions) and disruptive behaviors (e.g., aggression, screaming) have been reported to be the most burdensome to caregivers (Miyamoto et al., 2010; Rocca et al.,

2010; Huang et al., 2011). In addition to BPSD, certain characteristics of caregivers are known to determine the risk of burden including overload, quality of the relationship with the patient, adverse life events, gender, level of neuroticism, role captivity, and levels of confidence (Campbell et al., 2008).

In MCI subjects, comorbid neuropsychiatric symptoms have been associated with worse cognitive performance, mild extrapyramidal signs, and functional disability (Monastero et al., 2009). Depressive symptoms in subjects with MCI have also been linked to progression to dementia (Modrego and Ferrández, 2004; Gabryelewicz et al., 2007) and increased brain atrophy over 2 years (Lee et al., 2012) suggesting that they may represent an early sign of a neurodegenerative disease.

SYMPTOMS INTERRELATION AND EVOLUTION

The unitary concept of BPSD encompassing the full range of emotional, psychological, and behavioral abnormalities occurring in dementia reflects the clinical heterogeneity and complexity of the symptoms and the difficulty in characterizing more specific sub-syndromes or proprieties clusters co-varying during the course of the disease. Several studies have tried to identify neuropsychiatric sub-syndromes by grouping a number of individual symptoms which contingently co-occur during the course of dementia (Table 1). Ultimately, the recognition of discrete clinical entities is important to disclose underlying causal mechanisms and to develop etiological-based therapeutic interventions, even if the precise delineation of each syndrome remains elusive.

Although these studies differ in respect to study designs, assessment tools, and the size of samples, there is also a degree of concordance between the neuropsychiatric syndromes found (Table 1). Thus, delusions and hallucinations have been consistently grouped in a “*psychosis*” sub-syndrome in all factor analytical studies using the NPI. A distinct “*mood*” or “*affective*” cluster (depression and anxiety) has been reported by some studies (Aalten et al., 2007; Zuidema et al., 2007; Dechamps et al., 2008; Savva et al., 2009; Kang et al., 2010; Spalletta et al., 2010), while these symptoms have been included in different sub-syndromes by other authors (e.g., psychosis, agitation; Fuh et al., 2001; Mirakhor et al., 2004). A less reliable factor characterized by high levels of *agitation, aggression, and aberrant motor behavior* has emerged in several studies under various names (e.g., agitation, hyperactivity, frontal) (Frisoni et al., 1999; Aalten et al., 2003) presenting with heterogeneous psychopathological structure and suggesting that psychomotor features co-occur with psychotic and/or affective symptoms. There is evidence that “*psychosis*,” “*affective*,” and “*agitation/aggression*” factors remain stable across a 31-month period (Selbæk and Engedal, 2012).

The debate about the definition of the several psychiatric and behavioral symptoms in dementia continues as a number of symptoms (apathy, sleep, and eating disturbances) have not been grouped consistently across studies. Particularly, the relation between apathy (highly prevalent in dementia) and the “*mood*” sub-syndrome remains unclear. Studies conducted on outpatients (Aalten et al., 2008; Spalletta et al., 2010) and in nursing-homes (Zuidema et al., 2007; Dechamps et al., 2008; Selbæk and Engedal, 2012) support that apathy and depression are distinct phenomena

and belong to different neuropsychiatric syndromes. However, other studies group both symptoms in the same factor (Frisoni et al., 1999; Aalten et al., 2003; Hollingworth et al., 2006).

These discrepancies may result from the fact that individual symptoms evolve differently over the course of dementia. For example, as shown by a large cross-sectional study involving 3404 subjects, while apathy increases linearly with cognitive decline, the relations between BPSD and level of cognitive impairment are non-linear with higher prevalence rates observed in the middle stages of dementia (Lövhem et al., 2008). Several other cross-sectional studies in both community and institutionalized populations reported that greater cognitive impairment or dementia severity is associated with higher rates of some BPSD (Table 2). Yet, other studies were in disagreement with these findings and a systematic review found a lack of association between the severity of dementia and the prevalence of depressive symptoms or diagnosed depression (Verkaik et al., 2007). Psychotic (Scarmeas et al., 2005; Emanuel et al., 2011) and depressive symptoms (Chan et al., 2011) were reported to predict a faster cognitive deterioration.

There is limited information about the natural history and course of neuropsychiatric symptoms in MCI. In this context, Ryu et al. (2011) have concluded that neuropsychiatric symptoms in MCI usually persist, with a significant percentage of patients having at least one persistent symptom. These symptoms were more severe at baseline (Ryu et al., 2011). On the other hand, the presence of specific symptoms can aggravate cognitive decline; patients who present with both amnesic-MCI and apathy, but not those with depression, had an almost seven-fold risk of AD progression compared to amnesic-MCI patients without apathy, after adjustment of variables (Palmer et al., 2010).

Longitudinal studies provided further insight into the evolution of BPSD during the course of the disease (Table 3). In the Maastricht Study of Behavior in Dementia (MAASBED) patients with mild dementia at baseline showed more neuropsychiatric symptoms, whereas patients with severe dementia showed fewer neuropsychiatric symptoms throughout 2 years (Aalten et al., 2005b). Overall, BPSD tend to be present chronically and most patients with baseline symptoms continue to show at least one symptom at subsequent assessments. In the population-based Cache County Study, 67% of dementia subjects with clinically significant symptoms presented at least one symptom both at baseline and at 18 months follow-up assessment, with delusions and depression being the most persistent (Steinberg et al., 2004). In the MAASBED study 65% of outpatients who had a clinically relevant NPI total score at baseline continued to experience problems during the 2-year study period, with the most persistent symptoms being apathy and aberrant motor behavior (Aalten et al., 2005a). Persistence rates over 16 months were highest for delusions, agitation, depression, disinhibition, irritability, and aberrant motor behavior in a study conducted in nursing homes (Bergh et al., 2011). Repeated assessments have clarified that individual symptoms have an intermittent course, with elevated resolution and incidence rates throughout the time. Thus, one-third of patients with delusions, hallucinations, disinhibition, and agitation were symptom-free in the following 4 months (Bergh et al., 2011). Although it appears that BPSD have a heterogeneous pattern during the course of dementia, it has been proposed, especially in

Table 1 | Neuropsychiatric sub-syndromes reported in patients with dementia.

Reference	Sample/methods	Clusters
Devanand et al. (1992)	106 AD patients (outpatient clinic) BSSD	<i>Disinhibition</i> <i>Apathy-indifference</i> <i>Dependency motor agitation</i> <i>Self-destructive behaviors</i>
Hope et al. (1997)	97 AD or VaD patients (community) PBE, PCA	<i>Overactivity</i> : walking more, aimless walking, trailing or checking <i>Aggressive behavior</i> : aggressive resistance, physical aggression, verbal aggression and hostility <i>Psychosis</i> : hallucinations, persecutory ideas, anxiety
Harwood et al. (1998)	151 AD patients (outpatient clinic) BEHAVE-AD, PCA	<i>Agitation/anxiety</i> : agitation, anxiety of upcoming events, other anxiety <i>Psychosis</i> : delusions of theft, suspiciousness/paranoia, visual hallucinations <i>Aggression</i> : verbal aggression, physical treats/violence, fear of being left alone, other delusions <i>Depression</i> : tearfulness, depressed mood <i>Activity disturbance</i> : wandering, delusion one's house is not one's home
Frisoni et al. (1999)	162 AD patients (hospital) NPI, PCA	<i>Mood syndrome</i> <i>Psychosis syndrome</i> <i>Frontal syndrome</i>
Fuh et al. (2001)	320 AD + 212 VaD patients (outpatient clinic) NPI, FA	<i>Mood and psychosis</i> <i>Psychomotor regulation</i> <i>Social engagement</i>
Lyketsos et al. (2001)	198 AD patients (community) NPI, LCA	<i>Minimally symptomatic</i> <i>Affective disturbance</i> (depression, irritability, anxiety euphoria) <i>Psychotic disturbance</i> (delusions, hallucinations)
Aalten et al. (2003)	199 dementia patients (outpatient clinic) NPI, PCA	<i>Hyperactivity</i> : agitation, euphoria, irritability, disinhibition, aberrant motor behavior <i>Mood/apathy</i> : depression, apathy, sleep, appetite <i>Psychosis</i> : delusions, hallucinations, anxiety
Mirakhor et al. (2004)	435 AD patients (outpatient clinic) NPI, PCA	<i>Affect</i> : depression/dysphoria; anxiety; irritability; agitation/aggression <i>Physical behavior</i> : apathy; aberrant motor behavior; sleep disturbance; appetite/eating disturbance <i>Psychosis</i> : delusions; hallucinations <i>Hypomania</i> : disinhibition; elation/euphoria
Schreiner et al. (2005)	133 dementia patients (chronic care hospital) BEHAVE-AD, PCA	<i>Agitation</i> <i>Affective disturbance</i> <i>Altered circadian rhythms</i>
Matsui et al. (2006)	140 AD patients (outpatient clinic) NPI, FA	<i>Psychosis</i> : delusions, hallucinations, anxiety, agitation, disinhibition, irritability, aberrant motor activity <i>Mood</i> : apathy, depression/euphoria <i>Euphoria</i> : euphoria
Hollingworth et al. (2006)	1120 AD patients (community + nursing homes) NPI, PCA	<i>Behavioral dyscontrol</i> : euphoria, disinhibition, aberrant motor behavior, sleep, appetite <i>Psychosis</i> : delusions, hallucinations <i>Mood</i> : depression, anxiety, apathy <i>Agitation</i> : irritability, aggression
Aalten et al. (2007) Aalten et al. (2008)	2354/2808 AD patients (outpatient clinic) NPI, PCA	<i>Hyperactivity</i> : agitation; euphoria; disinhibition; irritability; aberrant motor behavior <i>Psychosis</i> : delusions; hallucinations; night time behavior disturbance <i>Affective symptoms</i> : depression; anxiety <i>Apathy</i> : apathy; appetite/eating abnormalities

(Continued)

Table 1 | Continued

Reference	Sample/methods	Clusters
Zuidema et al. (2007)	1437 dementia patients (nursing homes) NPI, FA	GDS 4/5: <i>Factor 1:</i> agitation, disinhibition, irritability, delusions <i>Factor 2:</i> depression, anxiety, delusions, hallucinations, aberrant motor behavior, night time behavior <i>Factor 3:</i> apathy, eating disorders <i>Factor 4:</i> euphoria GDS 6 <i>Factor 1:</i> agitation, disinhibition, irritability, euphoria <i>Factor 2:</i> depression, anxiety <i>Factor 3:</i> delusions, hallucinations <i>Factor 4:</i> aberrant motor behavior, night-time behavior <i>Factor 5:</i> apathy, eating disorders GDS 7: <i>Factor 1:</i> agitation, irritability <i>Factor 2:</i> delusions, hallucinations, disinhibition <i>Factor 3:</i> depression, anxiety <i>Factor 4:</i> apathy, aberrant motor behavior <i>Factor 5:</i> night-time behavior, eating disorders
Dechamps et al. (2008)	109 dementia patients (nursing homes) NPI, PCA	<i>Hyperactivity:</i> agitation, euphoria, disinhibition and irritability <i>Affective:</i> depression, anxiety, and eating change <i>Psychosis:</i> delusions, apathy and aberrant motor behavior <i>Hallucinations:</i> hallucination and sleeping disturbances
Savva et al. (2009)	587 AD patients (community) GMS, FA	<i>Factor 1:</i> psychosis, apathy and wandering <i>Factor 2:</i> anxiety and depression <i>Factor 3:</i> irritability, persecution, agitation <i>Factor 4:</i> elated mood, sleep disorder, hallucinations, agitation and wandering
Kang et al. (2010)	778 AD patients (hospital) NPI, FA (exploratory and confirmatory)	<i>Hyperactivity:</i> agitation/aggression; disinhibition; irritability <i>Affect:</i> depression; anxiety <i>Psychosis:</i> delusions; hallucinations <i>Apathy/vegetative symptoms:</i> apathy; sleep; appetite
Prado-Jean et al. (2010)	319 dementia patients (nursing homes) NPI, PCA	<i>Factor 1:</i> disinhibition, irritability, agitation, anxiety <i>Factor 2:</i> sleep disorder, aberrant motor behavior, apathy <i>Factor 3:</i> Euphoria, hallucinations, delusions <i>Factor 4:</i> Appetite and eating
Garre-Olmo et al. (2010b)	491 AD patients (outpatient clinic) NPI, FA (exploratory and confirmatory)	<i>Psychotic:</i> hallucinations, delusions <i>Affective:</i> depression, anxiety, irritability, agitation <i>Behavior:</i> euphoria, disinhibition, apathy, aberrant motor behavior
Spalletta et al. (2010)	1015 AD patients (outpatient clinic) NPI, PCA	<i>Psychomotor:</i> agitation, irritability, aberrant motor behavior. <i>Psychosis:</i> delusions, hallucinations <i>Affective:</i> anxiety, depression <i>Maniac:</i> euphoria, disinhibition <i>Apathetic:</i> apathy
Selbæk and Engedal (2012)	895 dementia patients (nursing homes) NPI, PCA	<i>Agitation:</i> agitation, euphoria, disinhibition, irritability, aberrant motor behavior, night-time behavior <i>Psychosis/affective:</i> delusions, hallucinations, depression, anxiety <i>Apathy/appetite:</i> apathy, appetite

AD, Alzheimer disease; BSSD, behavioral syndromes scale for dementia; GMS, geriatric mental state; LCA, latent class analysis; NPI, neuropsychiatric inventory; NPI-NH, neuropsychiatric inventory-nursing home version; PBE, present behavioral examination; PCA, principal component analysis; VaD, vascular dementia.

Table 2 | BPSD and dementia severity: cross-sectional studies.

Reference	Sample	Findings
Aalten et al. (2008)	2808 AD patients (outpatient clinic)	<i>Psychosis</i> and <i>hyperactivity</i> co-occurred more often in more severe stages of dementia.
Cheng et al. (2009)	138 (outpatient clinic) + 173 (long-term care) AD patients	Severity of <i>delusion/paranoid ideation</i> , <i>hallucination</i> , <i>activity disturbances</i> , <i>aggressiveness</i> , <i>diurnal rhythm disturbance</i> and <i>behavioral problems</i> significantly associated with severity of dementia.
Craig et al. (2005)	435 AD patients (hospital)	<i>Depression/dysphoria</i> and <i>apathy/indifference</i> more frequent in less severe dementia; hallucinations, elation/euphoria, and aberrant motor behavior more frequent in severe dementia. <i>Apathy</i> was the most persistent symptom; psychotic symptoms, delusions, and hallucinations exhibited the most rapid disappearance over time.
Di Iulio et al. (2010)	119 AD + 68 multidomain-MCI + 58 amnesic-MCI + 107 controls	<i>Apathy</i> more prevalent with increasing severity of cognitive syndromes (amnesic-MCI to multidomain-MCI, to AD). <i>Depression</i> prevalence increased from amnesic-MCI to multidomain-MCI, but not with dementia. No association with <i>night-time disturbances</i> .
Fernández Martínez et al. (2008a)	37 AD + 28 VaD patients (hospital, outpatient clinic)	<i>Behavioral changes</i> without correlation with severity of dementia in AD. Severity of <i>delusions</i> , <i>hallucinations</i> , <i>aggression</i> , <i>irritability</i> , <i>aberrant motor behavior</i> , <i>night-time behavior</i> and <i>appetite changes</i> correlated to cognitive decline in VaD.
Fernández Martínez et al. (2008b)	81 AD + 14 VaD + 10 PLBD + 3FTD (community)	Prevalence of neuropsychiatric symptoms increased with dementia severity, but was not statistically significant.
Fernandez-Martinez et al. (2010)	344 AD + 91 MCI + 50 controls (hospital, outpatient clinic)	All behavioral disorders increased with cognitive impairment, <i>except for sleep and appetite disorders</i> .
Fuh et al. (2005)	320 AD + 212 VaD patients (hospital, outpatient clinic)	<i>Delusions</i> , <i>hallucinations</i> , and <i>aberrant motor activities</i> more common in later stages in both AD and subcortical VaD.
García-Alberca et al. (2010)	125 AD patients (outpatient clinic)	No predictive value for MMSE in BPSD.
Geda et al. (2004)	87 AD + 54 MCI + 514 controls	Total NPI scores significantly different among the 3 groups.
Lopez et al. (2003)	1155 AD patients	Psychiatric symptoms, <i>except major depression</i> , more frequent in more severe stages of the dementia.
Lövheim et al. (2008)	3040 residents in geriatric care centers	Higher prevalence rates of BPSD in the middle stages of dementia. <i>Passiveness</i> increased linearly with the severity of cognitive impairment.
Lyketsos et al. (2000)	329 dementia patients (community)	Severity of dementia associated with increased prevalence of <i>agitation/aggression</i> (13% in mild dementia, 24% in moderate dementia, and 29% in severe dementia) and <i>aberrant motor behavior</i> (9% in mild, 17% in moderate, and 19% in severe dementia).
Matsui et al. (2006)	140 AD patients (outpatient clinic)	<i>Psychosis</i> and <i>agitated behaviors</i> co-occurred with dementia progression.
Spalletta et al. (2010)	1015 AD patients (outpatient clinic)	Poor association between cognitive deficits and severity of BPSD symptoms.
Thompson et al. (2010)	377 AD + 74 VaD patients (outpatient clinic)	Association between severity of BPSD and severity of dementia

(Continued)

Table 2 | Continued

Reference	Sample	Findings
Youn et al. (2011)	216 AD patients (hospital, outpatient clinic)	Neuropsychiatric symptoms more frequent in moderate-to-severe stages of AD, except <i>loss of enjoyment</i> and <i>social withdrawal</i> (more frequent in mild stages). Frequencies of all neuropsychiatric syndromes significantly different in relation to the severity of disease, except for <i>vegetative symptom</i> . <i>Inertia</i> showed the highest frequency in mild stages.
Zuidema et al. (2010)	1289 dementia patients (nursing homes)	Dementia severity predicted <i>physically aggressive behavior</i> and <i>apathy</i> , with higher prevalence in more severe stages of dementia.

NPI, neuropsychiatric inventory; *BPSD*, behavior and psychological symptoms of dementia; *MCI*, mild cognitive impairment; *AD*, Alzheimer disease; *VaD*, vascular dementia; *RAVLT*, Rey auditory verbal learning test; *TMT*, trail-making test; *MMSE*, mini mental state examination; *PLBD*, Parkinson–Lewy body dementia.

AD, that distinct groups of patients can be identified based on progressive changes in the frequency and severity of their BPSD (Garre-Olmo et al., 2010c).

In conclusion, instead of being independent phenomena, BPSD occur in a psychopathological pattern partially resembling primary psychiatric disorders, supporting a syndrome approach to their study and management. However, the psychopathological profile of each sub-syndrome is highly variable across patients (Savva et al., 2009). Also, the co-occurrence of sub-syndromes is common reflecting the complex and multi-level interaction between each BPSD (Dechamps et al., 2008) and supporting a personalized approach to each patient.

ALZHEIMER'S DISEASE VS. OTHER DEMENTIA TYPES

Although the manifestations of BPSD may be influenced by a variety of factors, they are primarily the result of the ongoing pathophysiological brain changes. It would be reasonable to assume that, as with the clinical and neuropsychological features, different profiles of neuropsychiatric symptoms could emerge in each sub-type of dementia, even at early stages. Thus, a higher prevalence of hallucinations and sleep disorders has been reported in non-amnesic-MCI, more likely to progress to non-AD dementia, in comparison to amnesic-MCI (Rozzini et al., 2008). However, studies comparing the profile of BPSD in AD and non-Alzheimer dementia have not yielded entirely uniform results (Tables 4 and 5).

ALZHEIMER DISEASE VS. VASCULAR DEMENTIA

The most consistent finding from the studies comparing vascular dementia (VaD) with AD is a higher prevalence and severity of depression and anxiety, similar rates of psychotic symptoms, and less severe aberrant motor behavior among subjects with VaD, although a substantial overlap can exist between the two dementia syndromes (Table 4). Similarly, the type of underlying vascular disease seems to determine a different clinical profile in VaD as apathy, aberrant motor behavior, and hallucinations have been associated with small-vessel VaD, whereas euphoria and agitation/aggression were more severe among patients with large-vessel VaD (Staekenborg et al., 2010).

ALZHEIMER DISEASE VS. DEMENTIA WITH LEWY BODIES

Studies comparing the clinical profile of autopsy-confirmed cases of DLB and AD have consistently found a higher prevalence of

delusions (misidentification, theft) and hallucinations (usually visual) in DLB patients independently of gender, ethnicity, and degree of cognitive impairment (Rockwell et al., 2000). These symptoms occur in up to 80 and 60% of patients respectively and tend to be more persistent over the course of the disease compared with AD patients (Ballard et al., 2001; Chiu et al., 2006; Stavitsky et al., 2006).

ALZHEIMER DISEASE VS. FRONTO-TEMPORAL LOBAR DEGENERATION

Fronto-temporal lobar degeneration (FTLD) is the prototype of a neurodegenerative disorder where changes in behavior, rather than in cognitive function, are the presenting feature and dominate the clinical picture throughout the disease course. The clinical spectrum of FTLD encompasses three distinct syndromes. The most common fronto-temporal dementia (also known as behavioral variant of fronto-temporal dementia) presents with a dramatic change in personal and social behavior. Early changes in language function are observed in semantic dementia and primary progressive non-fluent aphasia (Neary et al., 2005). Stereotypic behavior, appetite changes, and loss of social awareness are characteristic of FTLD with complex ritualized behaviors occurring more frequently in patients with fronto-temporal and semantic dementia than in AD (Bozeat et al., 2000; Ikeda et al., 2002). In contrast, simpler verbal stereotypes/perseveration or stimulus bound behavior, such as echolalia, seem to be equally common across the three groups (Nyatsanza et al., 2003). According to Bathgate et al. (2001) features that best discriminate FTLD from other dementias consist in loss of basic emotions, food cramming, pacing a fixed route, preserved capacity of locating objects, and impaired insight. Some behavioral features, such as lack of pain awareness, although not so common, provide diagnostic specificity as they are only rarely seen in other sub-types of dementia (Bathgate et al., 2001). Using the BEHAVE-AD scale, Chiu et al. (2006) found that AD outpatients presented with an increased incidence of anxiety and phobias (61.2%) whereas subjects with fronto-temporal dementia had higher levels of activity disturbances (92.3%).

OTHER FACTORS ASSOCIATED WITH BPSD

Besides the influence of dementia stage and subtype on the emergence of BPSD, other factors such as demographic variables and the use of medication have not been extensively explored. A number of associations, albeit not consistently replicated,

Table 3 | BPSD evolution: longitudinal studies.

Reference	Follow-up	Findings
Aalten et al. (2005a)	2 years (each 6 months)	No significant changes over time in the three sub-syndromes or in the NPI total score. <i>Depression</i> became less common, persistent and severe with disease progression. <i>Apathy</i> increased from the second visit (after six months), and persisted during the more advanced stages of dementia. <i>Psychosis</i> (delusions) was most common in the moderate stages, showing low persistence over time.
Aalten et al. (2005b)		Mild dementia at baseline predicted increasing prevalence of NPS with time, whereas the reverse was observed with severe dementia. Presence of NPI symptoms at baseline predicted the subsequent development of symptoms (especially mood/apathy). Hyperactivity predicted the development of psychosis but not vice-versa.
Bergh et al. (2011)	16 months (each 4 months)	Highest cumulative incidence for <i>irritability</i> (42.6%), <i>disinhibition</i> (37.8%) and <i>depression</i> (31.5%). High persistence for Delusions, agitation, depression, disinhibition, irritability and aberrant motor behavior. No significant change in the severity of the NPS during the follow-up period.
Garre-Olmo et al. (2010c)	24-months	Increase of psychotic and behavioral symptoms (18–26% and 63–72%, respectively). Affective symptoms remained stable over the follow-up.
Savva et al. (2009)	2 years	Presence of <i>apathy</i> , <i>elated mood</i> or <i>confabulation</i> at follow-up was not significantly linked to their presence at baseline. Conversely, <i>anxiety</i> , <i>depression</i> , and <i>wandering behavior</i> at baseline were strong indicators for their presence at follow-up. Anxiety, depression, and elation did not tend to persist. Symptoms of <i>psychosis</i> were more persistent.
Selbaek et al. (2008)	12-month	Symptoms were chronically present, although individual symptoms often showed an intermittent course with higher resolution for <i>depression</i> (58%), <i>delusions</i> (56%), and <i>agitation/aggression</i> (47%).
Selbæk and Engedal (2012)	31 months	The most stable co-occurring symptoms in one and the same factor were depression and anxiety (<i>affective</i>), agitation, irritability, and disinhibition (<i>agitation</i>), delusions and hallucinations (<i>psychosis</i>), and apathy and appetite disorder.
Serra et al. (2010b)	12 months	Frequency and severity of dysphoria/depression, apathy, agitation/aggression, and anxiety remained substantially the same at follow-up. Delusions and irritability/lability increased significantly.
Steinberg et al. (2004)	18 months	Delusions and depression were the most persistent, while disinhibition was the least.
Tschanz et al. (2011)	3.8 years Drop-out: 29%	Increasing occurrence, rate, and overall severity of NPS over time. Rate of change in NPS was weakly correlated with rate of change in cognition or function.
Wancata et al. (2003)	6 months Drop-out: 26.9%	While, at T1, 33.7% suffered from any marked or severe non-cognitive symptoms, 11.6% remitted from these symptoms within 6 months.
Weamer et al. (2009)	2 years	Greater global cognitive impairment was present at base line in subjects who developed psychosis at follow-up.
Wetzels et al. (2010)	2 years	Agitation, irritability, and aberrant motor behavior were the most prevalent over the 2 years. Affective symptoms decreased, apathy tended to increase. Agitation and aberrant motor behavior were the most persistent symptoms.

have been described between neuropsychiatric symptoms, and patient-related or environmental factors.

PATIENT-RELATED FACTORS

Demographic factors

Aggressiveness or aberrant motor behavior has been more frequently reported in men with dementia whereas female gender has

been associated with depressive/anxious symptoms and verbally agitated help-seeking behavior (Lövhelm et al., 2009; Zuidema et al., 2010; Karttunen et al., 2011). In one study, female elderly with VaD had more neuropsychiatric symptoms than male elderly (Hsieh et al., 2009). In other studies, age and gender did not influence the likelihood of BPSD manifestation in AD or VaD (Savva et al., 2009; Di Iulio et al., 2010; Staekenborg et al., 2010).

Table 4 | BPSD: Alzheimer's disease vs. vascular dementia.

Reference	Sample	Findings
Aharon-Peretz et al. (2000)	30 AD + 30 VaD	Aggression, depression, anxiety and apathy significantly more severe in VaD-WSI than in AD.
Ballard et al. (2000a)	92 AD + 92 VaD	Depression and anxiety more common in VaD than in AD. Psychotic symptoms similarly common in VaD and in AD.
Chiu et al. (2006)	85 AD + 32 VaD	VaD with higher incidence of paranoid and delusional ideation and affective disturbance.
Fernández Martínez et al. (2008a)	37 AD + 28 VaD	Sleep disturbances and appetite changes more prevalent in AD than in VaD. Aberrant motor activity more common in subcortical VaD.
Fernández Martínez et al. (2008b)	81 AD + 14 VaD	Similar prevalence of BPSD in AD and VaD.
Fuh et al. (2005)	320 AD + 212 VaD	Similar prevalence in AD, cortical VaD, sub-cortical VaD, and mixed VaD. More severe sleep disturbance in cortical VaD than in AD.
Hsieh et al. (2009)	77 AD + 77 VaD	Higher prevalence of night-time behavior (sleep disturbance) in AD; higher prevalence of depression in VaD. Similar prevalence of delusions, hallucinations, and agitation in AD and VaD
Ikeda et al. (2004)	21 AD + 28 VaD	Delusions and aberrant motor behavior more likely in AD.
Kim et al. (2003)	99 AD + 36 VaD	Depression and anxiety significantly more severe in VaD than in AD.
Lyketsos et al. (2000)	214 AD + 62 VaD	Delusions more likely in AD and depression more frequent in VaD.
Lyketsos et al. (2002)	258 AD + 104 non-AD	Similar prevalence in AD and non-AD dementia, except for more frequent aberrant motor behavior in AD.
Srikanth et al. (2005)	44 AD + 31 VaD	Similar symptom profile in AD and in VaD.
Thompson et al. (2010)	377 AD + 74 VaD	No significant difference in AD and VaD patients on the BPCL or on the RMBPCL.

AD, Alzheimer disease; VaD, vascular dementia; VaD-WSI, ischemic white matter subcortical changes and lacunar infarctions; BPCL, behavior problems check list; RMBPCL, revised memory and behavior problems check list.

Table 5 | BPSD: Alzheimer's disease vs. fronto-temporal lobar degeneration.

Reference	Sample	Findings
Bathgate et al. (2001)	30 FTD + 75 AD + 34 VaD	Loss of basic emotions, food cramming, pacing a fixed route, an absence of difficulty in locating objects, and an absence of insightfulness differentiated FTD from other dementias.
Bozeat et al. (2000)	13 FTD + 20 SD + 37 AD	Stereotypic and eating behavior and loss of social awareness more common in the FTD group. Mental rigidity and depression more frequent in SD than in FTD. Patients with FTD more disinhibited.
Chiu et al. (2006)	17 FTD + 85 AD + 32 VaD	Higher incidence of activity disturbances in FTD.
Fernández Martínez et al. (2008b)	3 FTD + 81 AD + 14 VaD	Higher aberrant motor activity prevalence in FTD.
Ikeda et al. (2002)	23 FTD + 25 SD + 43 AD	Changes in eating behaviors more common in both FTLT groups compared with AD.
Levy et al. (1996)	22 FTD + 30 AD	Higher scores for disinhibition, apathy, aberrant motor behavior, and euphoria in patients with FTD compared with AD.
Nyatsanza et al. (2003)	18 FTD + 13 SD + 28 AD	Complex ritualized behaviors were significantly more frequent in patients with fvFTD and semantic dementia than in AD.
Srikanth et al. (2005)	23 FTLT + 44 AD + 31 VaD	Disinhibition, aberrant motor behavior, and appetite/eating disturbances could reliably differentiate AD and VaD from FTLT.

AD, Alzheimer disease; FTLT, fronto-temporal lobar degeneration; FTD, fronto-temporal dementia; SD, semantic dementia.

Considering that most studies included white population from northern European descent it's difficult to make assumptions about whether different symptom profile may arise according to ethnicity as reported by a few studies (Chen et al., 2000; Chow et al., 2002). In the study by Kim et al. (2003), age of onset and duration of dementia did not show any significant correlation with BPSD in patients with AD or VaD. Toyota et al. (2007) found conversely that early onset AD patients showed fewer BPSD than their late onset counterparts, particularly delusions, hallucinations, agitation, disinhibition, and aberrant motor behavior although this was not confirmed by a recent study (Garre-Olmo et al., 2010a).

Psychotropic medication

Aggressiveness and psychotic symptoms in outpatients with dementia have been found to increase the likelihood of receiving psychotropic medications by at least two-fold and this was coupled with a higher caregiver burden (Chiu et al., 2006). However, conclusions regarding the effects of medication on the natural course of BPSD are unclear as most studies don't have available data concerning the usual treatment of patients or don't include sub-analysis regarding this variable. Aalten et al. (2008) reported that the use of cholinesterase inhibitors (ChEI) influenced the structure of the apathy factor. Although this finding could derive from a therapeutic effect the available evidence suggests a modest impact of these drugs on neuropsychiatric symptoms (Rodda et al., 2009). The same holds true for antipsychotics which have been found to have little effect on the sub-syndrome factor structure of BPSD (Aalten et al., 2008).

Psychopathological symptoms

Depression affects up to 43% of patients with dementia and it predicts an increased number of neuropsychiatric symptoms, particularly agitation, anxiety, and irritability (Prado-Jean et al., 2010). Lack of insight occurs in the majority of AD patients even in early stages and appears to be an important predictive factor for the occurrence of increased levels of neuropsychiatric symptoms including apathy, agitation, irritability, psychosis, or behavioral symptoms in general (Vogel et al., 2010).

Neuropsychological deficits

The presence of alterations in specific cognitive domains may have a predictive value for the occurrence of BPSD. Psychotic symptoms in AD patients have been found to correlate with impairments in verbal fluency (Tsai et al., 2010) and in verbal learning tasks (Starr and Lonie, 2007). Premorbid IQ has been proposed to mediate the relationship between BPSDs and cognition in AD as it significantly correlated with mood, frontal, and psychotic factors (Starr and Lonie, 2007). In a cross-sectional study, impairments in memory (episodic and semantic), executive function, and verbal fluency all correlated with the severity of neuropsychiatric symptoms (García-Alberca et al., 2010). The presence of specific neurocognitive deficits, such as executive dysfunction, was reported to predict greater BPSD symptom severity in patients with MCI, particularly of depression and anxiety (Rosenberg et al., 2011).

ENVIRONMENTAL FACTORS

Presence of neuropsychiatric symptoms may arise from the characteristics of psychosocial/physical environment, such as crowded

housing conditions leading to sensory overstimulation (for which patients with dementia are more susceptible), attitudes of care staff toward challenging behaviors and/or the size of the units in which patients reside throughout the day (Zuidema et al., 2010). Similarly, patients being restrained, or subjected to multiple moves and procedures, may also contribute to a range of BPSD symptoms, especially wandering and aggression (Kunik et al., 2010).

PATHOPHYSIOLOGY AND NEUROBIOLOGY OF BPSD

The behavioral or psychological disturbances occurring in dementia can be understood as ineffective attempts of the patient to cope with environmental or physiological stress factors. Indeed, BPSD are also common in non-demented older adults with rates of 5.6% for anxiety, 4.5% for irritability and 2.8% for agitation/aggression (Lyketsos et al., 2000) while psychotic symptoms are present in up to 10.5% of Swedish 85 years-old people (Ostling et al., 2009). It is important, therefore, to trace back these symptoms to premorbid psychosocial functioning which is determined by constitutional factors (e.g., personality traits, cognitive styles, and emotional reactivity), past experiences and level of education. Abnormalities in the intensity, magnitude, duration, timing, and modifiability of internal conditions and/or observable behaviors are expected to emerge beyond the limits of normal variability as the ongoing neuropathological changes of dementia undermine the individual's usual psychological capacities to adequately respond to everyday demands. Defining these neuroanatomical and neurochemical correlates of BPSD has been an area of active research with a hope that clarification of the underlying neurobiology will lead to more effective treatments (Tables 6–8).

PSYCHOSIS

Not many studies have examined the neuropathological correlates of psychosis in AD. Two studies found an association of psychosis with increased severity of beta-amyloid senile plaques (SP) in the presubiculum (Zubenko et al., 1991) and across cortical regions (Mukaetova-Ladinska et al., 1995). Förstl et al. (1994) reported changes in neuronal counts in the CA1 hippocampus and parahippocampal gyrus, while Zubenko et al. (1991) described increased density of neurofibrillary tangles (NFT) in the middle frontal cortex. Furthermore, Farber et al. (2000) reported that AD patients with psychosis had a 2.3-fold greater density of neocortical NFTs than AD subjects devoid of psychotic symptomatology. However, no similar relation was observed in non-neocortical areas or with SP burden. On the other hand, no significant differences were found between AD patients with ($n = 24$) and without ($n = 24$) psychosis in respect to SP and NFT densities in the study by Sweet et al. (2000). Consistently with the neocortical role underlying psychotic symptomatology, AD subjects with psychosis demonstrated significant elevations of glycerophosphoethanolamine and significant reductions of *N*-acetyl-L-aspartate in temporal, frontal, and parietal cortices (Sweet et al., 2002).

Neuroimaging studies have similarly confirmed severe abnormalities in grey matter volume, cerebral blood flow, and metabolism in the above cortical regions of AD subjects with psychotic symptoms (reviewed in Casanova et al., 2011). Anatomically, these changes partially coincide with cholinergic and dopaminergic pathways supporting, together with neurochemical and

Table 6 | BPSD and structural changes in neuroimaging exams.

Symptoms	Findings	References	Sample
Delusional misidentification	<i>Computerized tomography</i> Right frontal and temporal atrophy	Förstl et al. (1994)	56 AD patients
Depression	<i>Magnetic resonance imaging</i> Decreased gray matter volume in right hippocampus and amygdala	Egger et al. (2008)	14 AD patients
Apathy	Anterior cingulate gyrus, orbitofrontal, and frontosubcortical areas atrophy	Tunnard et al. (2011) Bruen et al. (2008) Massimo et al. (2009)	111 AD patients 31 mild AD patients 40 FTLD patients
Delusions	Decreased GM volume in frontal, temporal, and limbic regions	Bruen et al. (2008) Massimo et al. (2009)	31 mild AD patients 40 FTLD patients
Visual hallucinations	Lesions on visual cortex and association areas detected in MRI	Holroyd et al. (2000)	14 AD patients
Agitation	Anterior cingulate cortex and left insula atrophy	Bruen et al. (2008)	31 mild AD patients
Aggressive behavior	Amygdala atrophy	Poulin et al. (2011)	264 AD patients
Disinhibition	Cingulate frontal cortex atrophy and medial orbital frontal cortex atrophy	Serra et al. (2010a) Massimo et al. (2009)	54 AD patients 40 FTLD patients
Anxiety, sleep disorders, and aberrant motor behavior	Increased WMH volume	Berlow et al. (2010)	37 AD patients

AD, Alzheimer disease; FTLD, fronto-temporal lobar degeneration; GM, gray matter; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

Table 7 | BPSD and functional changes in neuroimaging exams (PET and SPECT studies).

Symptoms	Findings	References	Sample
Depression	Hypoperfusion and hypometabolism in some areas of temporal, frontal, and parietal lobes	Hirono et al. (1998) Staffen et al. (2009)	53 AD patients 149 MCI + 131 DA + 127 DCI patients
Apathy	Decreased perfusion and hypometabolism in anterior cingulate gyrus, orbitofrontal, and frontosubcortical areas	Lanctôt et al. (2007b) Benoit et al. (1999) Marshall et al. (2007) Craig et al. (1996)	51 AD patients 63 AD patients 41 AD patients 31 AD patients
Psychosis	Hypometabolism in frontal lobe	Sultzer et al. (1995)	21 AD patients
Hallucinations	Hypoperfusion in parietal lobe	Kotrla et al. (1995)	30 AD patients
Delusions	Hypometabolism of prefrontal, anterior cingulate, right temporal, and parietal cortex Increased metabolism in the inferior temporal gyrus and decreased metabolism in the occipital lobe	Staff et al. (2000) Sultzer et al. (2003) Hirono et al. (1998)	45 AD patients 25 AD patients 65 AD patients
Agitation	Changes in metabolism in frontal and temporal cortices	Sultzer et al. (1995)	21 AD patients
Aggressive behavior	Hypoperfusion in the temporal cortex (right middle and left anterior)	Lanctôt et al. (2004) Hirono et al. (2000)	49 AD patients 10 dementia patients

AD, Alzheimer disease; MCI, mild cognitive impairment; FTLD, fronto-temporal dementia; DCI, depression with cognitive impairment (DCI).

Table 8 | Associations between BPSD and genes.

References	Gene	Sample	Pathway	Clinical correlates
Borroni et al. (2006)	COMT	232 AD patients	Dopamine	Higher risk for "psychosis" (ORs = 3.05, 2.38, and 1.80 for delusions, hallucinations, and sleep disturbance symptoms, respectively) $p < 0.05$
	5-HTTLPR		Serotonin	Lower risk for "frontal" endophenotype (ORs = 0.25 and 0.25 for disinhibition and euphoria, respectively). $P < 0.05$
	APOE4			Lower risk for "psychosis" (ORs = 0.32, 0.41, and 0.54 for disinhibition and euphoria, respectively) No correlation with any endophenotype
Angelucci et al. (2009)	5-HT2A receptor polymorphism (102T/C)	80 AD patients	Serotonin	Delusions associated with T allele ($p < 0.05$)
Di Maria et al. (2009)	G72 gene (locus DAO)	185 AD patients	Glutamate	Delusions and hallucination ($p < 0.05$)
Proitsi et al. (2012)	SERT STin2 12R	1008 AD patients	Serotonin	Less "psychosis" ($p = 0.025$) and less apathy ($p = 0.007$)
	DAT 10R		Dopamine	Increased agitation ($p = 0.003$) increased aberrant motor behavior ($p = 0.009$)
	DRD4 2R			Increased "moods" levels ($p = 0.004$); increased sleep abnormalities ($p = 0.032$)
	DRD1 G			Higher irritability ($p = 0.01$); lower aberrant motor behavior ($p = 0.023$)
	DRD3 Ball C			Lower depression ($p = 0.007$)

COMT, catechol-O-methyl transferase; 5-HTTLPR, serotonin gene-linked polymorphic region; APOE, apolipoprotein E; 5-HT2A, serotonin 2A receptor; DAO, D-amino acid oxidase; SERT STin2, serotonin transporter gene polymorphism STin2; DAT, dopamine transporter gene; DRD4, dopamine receptor 4; DRD1, dopamine receptor 1; DRD3, dopamine receptor 3 Ball polymorphism.

pharmacological evidence, the role of acetylcholine and dopamine imbalance in the pathogenesis of AD psychosis (reviewed in Pinto et al., 2011). Psychosis has also been associated with the relative preservation of norepinephrine in the substantia nigra and a significant serotonin reduction in the presubiculum (Ismail et al., 2011). A strong heritability has been reported for psychosis in AD, suggesting an important role for APOE4 (Ismail et al., 2011). Other genes have also been associated with higher risk of psychosis [(COMT, G72 gene (locus DAO); 5-HT2A receptor polymorphism (102T)] while others may be "protective" (5-HTTLPR, SERT STin2 12R; **Table 8**). In DLB, visual hallucinations have been linked to higher Lewy Body density in the temporal cortex and amygdala (Harding et al., 2002; Tsuang et al., 2009) and with less severe density of neocortical tangles (Ballard et al., 2004). Cholinergic deficits have been described for hallucinations and delusions in both AD (Tsang et al., 2008) and DLB (Ballard et al., 2000b; Teaktong et al., 2005), thus providing a rationale for the therapeutic use of cholinergic drugs to treat these symptoms.

DEPRESSION

Several lines of evidence suggest that depression shares complex pathophysiological routes with dementia. It has been hypothesized that chronic depression may accelerate neurodegenerative changes of AD as a result of the neurotoxic effects of elevated cortisol levels in the hippocampus (Korczyn and Halperin, 2009). Moreover, the observation that the late-life depressive disorders are commonly associated with increased number of white matter hyperdensities in subcortical areas supported the so-called "vascular hypothesis"

of depression (Alexopoulos, 2005). Reversely, neurodegenerative and vascular changes may act as a risk factor for depression.

Depressed non-demented patients present with chronic elevation of inflammatory mediators, known to play a central role in AD pathogenesis, together with altered serotonin metabolism and reduced neurotrophic activity (Caraci et al., 2010). So, in addition to being merely an emotional reaction to early memory deficits depression can be a prodromal symptom of dementia, a risk factor for neurodegeneration or co-occur with cognitive impairment. Post-mortem studies in AD subjects found higher burden of neuropathological lesions in those with a lifetime history of depression (Rapp et al., 2006) or presenting with concurrent depression (Rapp et al., 2008). Functional imaging studies revealed decreased perfusion and hypometabolism in the temporal, frontal, and parietal cortex, as well as in thalamus and lentiform nucleus of depressed compared to non-depressed AD patients (Hirono et al., 1998; Staffen et al., 2009). However, in other post-mortem studies in AD subjects with depressive symptoms were not related to the level of pathology (Wilson et al., 2003; Sweet et al., 2004).

The only prospective study assessing brain tissue from dementia-free subjects ($n = 153$) did not find increased AD or cerebrovascular pathology in those with late-life depression (Tsopelas et al., 2011), suggesting that depression *per se* may be linked to additional, more subtle neuropathological and/or neurobiochemical changes, such as those involving the neurotransmitter systems. Indeed, a disturbed serotonergic system has been associated with depressive symptoms in AD as several areas of the brain exhibit decreased serotonin concentration, with a significant

reduction in 5-HT₁ and 5-HT₂ receptors throughout the cerebral cortex (Lanari et al., 2006). Similarly, loss of noradrenergic cells in consequence of degeneration of the locus coeruleus is also seen in individuals with dementia who manifest depressive symptoms (Lanari et al., 2006). Changes of GABAergic plasma levels observed in final stages of AD have also been associated with depression, apathy, and aggressive behaviors (Lanctôt et al., 2007a). Association between genetic factors and depression are summarized in **Table 8**.

APATHY

Post-mortem and *in vivo* studies suggest that AD is associated with a dysfunctional dopaminergic system, since reduced levels of dopamine (DA) and homovanilic acid, as well as altered DA receptor density, have been described in discrete brain regions coinciding with the mesocorticolimbic pathway (Mitchell et al., 2011). On the other hand, neuroimaging studies in AD have been consistently showing a significant association between apathy and changes in the brain reward system including atrophy (Apostolova et al., 2007; Bruen et al., 2008; Tunnard et al., 2011), hypoperfusion and hypometabolism (Craig et al., 1996; Benoit et al., 1999; Lanctôt et al., 2007b; Marshall et al., 2007) in the anterior cingulate gyrus and orbitofrontal areas (**Tables 6, 7**). It is also possible that dysfunction in these areas underlies the reported relation between increased frontal white matter changes and apathy (Starkstein et al., 2009) together with disruption of deep white matter afferents and efferents to the basal ganglia and/or by decrement of metabolic activity in frontal subcortical regions. In FTD subjects, apathy has been associated with atrophy in the anterior cingulate cortex, right dorso-lateral prefrontal cortex (Massimo et al., 2009), and adjacent medial frontal cortex (Rosen et al., 2005). This suggests that dysfunction in the frontosubcortical cingulate pathways is implicated in apathy regardless of the sub-type of dementia.

OTHER SYMPTOMS

Increased burden of NFT in the orbitofrontal cortex has been linked to agitation (Tekin et al., 2001), while aggressive behaviors have been associated with neuronal loss in locus coeruleus (Matthews et al., 2002). Deterioration of brainstem regions and in the suprachiasmatic nucleus of the hypothalamus has been reported in patients with sleep disorders (Yesavage et al., 2003).

MANAGEMENT OF BPSD

Management of BPSD is a key component of a comprehensive approach to the treatment of dementia requiring the judicious combination of pharmacological and non-pharmacological interventions. Treatment of these symptoms remains problematic, with an increased risk of psychotropic medication misuse, and, thus, represents an important challenge for clinicians. Current guidelines recommend non-pharmacological interventions as first-line treatment followed by the least harmful medication for the shortest time possible (Gauthier et al., 2010; Azermai et al., 2011).

NON-PHARMACOLOGICAL INTERVENTIONS

Non-pharmacological interventions have been classified into the following categories (O'Neil et al., 2011): (i) cognitive/emotion-oriented interventions (reminiscence therapy, simulated presence

therapy, validation therapy); (ii) sensory stimulation interventions (acupuncture, aromatherapy, light therapy, massage/touch, music therapy, Snoezelen multisensory stimulation, transcutaneous electrical nerve stimulation); (iii) behavior management techniques; and (iv) other psychosocial interventions such as animal-assisted therapy and exercise. Unfortunately, despite efforts in investigating these interventions, consistent evidence about the efficacy of the various psychosocial therapies is lacking (Kong et al., 2009). Benefits from psycho-educational interventions for caregivers were documented to be long-lasting, especially when delivered individually (Livingston et al., 2005). Special care units have been developed since the 1980s and are commonly situated in nursing homes. They include the features of trained staffing, a modified physical environment, and family involvement (Lai et al., 2009).

Specific therapeutic interventions for different symptoms of BPSD have also been investigated. In relation to agitation and aggressive behavior, and before opting for any intervention, it is important to carefully analyze the causes for the disruptive behavior: such causes may include pain, medical illness, fatigue, depression, loneliness, understimulation, or overstimulation; and social and environmental stressors (Iwata et al., 1993; Salzman et al., 2008). Strategies reported to be useful to reduce agitation include sensory interventions, particularly music therapy (Choi et al., 2009), aromatherapy (Ballard et al., 2009), and environmental modification (Weitzel et al., 2011). Regarding depression, recent studies support the effectiveness of home-based exercise programs for people with dementia and their caregivers to reduce depressive symptoms (Prick et al., 2011). Recently animal-assisted activities were suggested to be associated with a decrease in anxiety and sadness and an increase in positive emotions and motor activity (Mossello et al., 2011).

PHARMACOLOGICAL INTERVENTIONS

A variety of medications have been used to treat BPSD including typical and atypical antipsychotics, antidepressants, anticonvulsant mood stabilizers, ChEI, benzodiazepines, and other drugs, such as memantine. These drugs have variable efficacy and effectiveness in treating BPSD, depending on the target symptom and class of medication. The pharmacological treatment of BPSD should consider the presence of additional comorbidities and associated medications, which increase significantly the risk of both medical complications and drug interactions. Current guidelines recommend careful consideration of both benefits and limitations of each drug class with the use of the least harmful medication for the shortest time possible (Gauthier et al., 2010).

Antipsychotics

The use of antipsychotics, particularly since the introduction of atypical antipsychotics, has increased over time (Briesacher et al., 2005). They have shown efficacy in treating specific symptoms, such as aggression, psychosis, and agitation (Ballard et al., 2008; Gauthier et al., 2010). However the evidence regarding other BPSD symptoms is not convincing (Ballard et al., 2008). Despite serious side effects, including extrapyramidal symptoms, sedation, tardive dyskinesia, gait disturbances, falls, anticholinergic side effects, cerebrovascular events, and increased mortality, antipsychotic are

still widely used off-label (Azermai et al., 2011). Risperidone, olanzapine, and haloperidol appear to be more effective for managing BPSD (Azermai et al., 2011). A recent study on dementia patients reported a 1.5-fold increase in mortality associated with the use of haloperidol, compared to risperidone, olanzapine or quetiapine. The mortality risk with haloperidol was highest during the first 30 days and decreased significantly over time (Kales et al., 2012). The use of an antipsychotic for severe symptoms such as agitation, aggression, and psychotic symptoms should be time-limited and a careful individual evaluation is recommended due to increased risk of stroke and mortality. In the UK, risperidone is licensed for up to 6 weeks treatment of persistent aggression in subjects with moderate-to-severe AD, and the recommendations are to be used as a last resort for aggression, when all other methods have failed to alleviate the most distressing symptoms of dementia, and only when it is in the best interests of the person (<https://www.alzheimers.org.uk/antipsychotics>). It is prudent to initiate with a low dose and regularly review the prescription in function of the patient's response and presence of adverse events.

Antidepressants

Antidepressants can be an effective and well-tolerated alternative to antipsychotics in vulnerable elderly individuals for treatment of BPSD (Henry et al., 2011). This class of drugs has been used primarily for depression, with efficacy especially for the selective serotonin reuptake inhibitors (SSRIs; Gauthier et al., 2010). Some authors found that citalopram and sertraline could improve symptoms of agitation and psychosis in subjects with dementia with similar efficacy, but better tolerability and safety, than haloperidol and risperidone (Gauthier et al., 2010; Seitz et al., 2011). Citalopram was effective in treating disinhibition, irritability and depression and also behaviors specific to FTD (Herrmann et al., 2011). However, the evidence so far does not support the use of these medications for BPSD other than depression (Azermai et al., 2011).

Cholinergic inhibitors

Current guidelines support the use of ChEI for BPSD although different recommendations exist to each specific drug (Gauthier et al., 2010). Donepezil, galantamine, or rivastigmine have all shown a modest effect on the broad spectrum of neuropsychiatric symptoms in AD (Rodda et al., 2009). They should be initiated prior to the use of other psychotropic agents since ChEIs reduce behavioral changes and improve or delay cognitive and functional decline (Gauthier et al., 2010). The behavioral symptoms most likely to improve with ChEIs treatment appear to be apathy, depression, and aberrant motor behavior (Cummings, 2004; Holmes et al., 2004; Feldman et al., 2005).

Memantine

Memantine, an NMDA receptor antagonist, can also have beneficial effects on behavior, as well as on cognition and function; however there is insufficient evidence to recommend its use (Azermai et al., 2011). The use of memantine appears to improve specific behaviors, such as agitation and irritability, which differ from

those affected by ChEIs (mood symptoms, apathy, and aberrant motor behavior). Combination therapy may have advantages in patients with multiple BPSD (Gauthier et al., 2010). The latest report on combined memantine and ChEIs (donepezil) treatment did not show any major advantages on cognitive and behavioral changes in subjects with moderate-to-severe AD, compared to those treated with either memantine or donepezil, with only negligible improvement on the NPI scores in the subjects treated with the combination of the two antidementia drugs (Howard et al., 2012).

Anticonvulsants

Anticonvulsant mood stabilizers such as carbamazepine, valproic acid, gabapentin, lamotrigine, topiramate are widely used in clinical practice. Treatment regimens with anticonvulsant mood stabilizers have shown promising results and seem to be beneficial for some dementia patients (Konovalov et al., 2008). Anticonvulsants may allow dose reduction of antipsychotics; however, investigation regarding benefits, safety, and tolerability of these drugs has produced mixed results, so they are not recommended for routine use. In particular sodium valproate has been shown to be ineffective in the treatment of agitation in AD, and has been associated with increased adverse effects, including falls, infection, and gastrointestinal disorders (Lonergan and Luxenberg, 2009).

Benzodiazepines

Benzodiazepines may be used at short-term for acute agitation or agitation associated with anxiety (Azermai et al., 2011).

CONCLUSION

Neuropsychiatric symptoms are frequent in dementia and contribute significantly for burden caregiver and illness costs. Correct identification and evaluation of these symptoms is a crucial part of the clinical approach to dementia. Despite the tentative efforts to group different symptoms into clusters (to facilitate clinical/diagnostic investigations), there is not yet an established model. The pathogenesis of these symptoms is not well understood, and the current knowledge supports multifactorial causes. Development and use of new specific investigation techniques may be helpful to better understand the underlying etiological mechanisms of various neuropsychiatric symptoms. At present, combination of non-pharmacological and appropriate pharmacological strategies represents the best treatment of BPSD. However, there is no consistent evidence about specific strategies for individual symptoms. It is necessary to encourage application of novel non-pharmacological interventions, which are safer than pharmacological therapies. Further investigation is similarly needed to find more effective, safe, and well-tolerated pharmacological therapies. This will help to devise novel, more symptom targeted, and specific interventions that will improve significantly the management of BPSD symptoms in subjects with dementia.

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