

## Title

Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease?

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## Running title

Behavioural and psychological symptoms of dementia in Down syndrome

## Abstract

Behavioural and Psychological Symptoms of Dementia (BPSD) are a core symptom of dementia and are associated with suffering, earlier institutionalization and accelerated cognitive decline for patients and increased caregiver burden. Despite the extremely high risk for Down syndrome (DS) individuals to develop dementia, BPSD have not been comprehensively assessed in the DS population. Due to the great variety of DS cohorts, diagnostic methodologies, sub-optimal scales, covariates and outcome measures, it is questionable whether BPSD have always been accurately assessed. However, accurate recognition of BPSD may increase awareness and understanding of these behavioural aberrations, thus enabling adaptive caregiving and, importantly, allowing for therapeutic interventions. Particular BPSD can be observed (long) before the clinical dementia diagnosis and could therefore serve as early indicators of those at risk, and provide a new, noninvasive way to monitor, or at least give an indication of, the complex progression to dementia in DS.

Therefore, this review summarizes and evaluates the rather limited knowledge on BPSD in DS and highlights its importance and potential for daily clinical practice.

## Keywords

Alzheimer's disease; BPSD; dementia; Down syndrome; neuropsychiatric symptoms

## 1. Introduction: Down syndrome and Alzheimer's disease – a disruptive marriage

Intellectual disability, previously referred to as mental retardation, is defined as 'a significantly reduced ability to understand new or complex information and to learn and apply new skills' (World Health Organization, 2014) and reaches a prevalence of approximately 1% in the Western population (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011). The most common genetic cause of human intellectual disability is Down syndrome (DS), caused by the triplication of the human chromosome 21 (HSA21). DS, or trisomy 21, is present in approximately 1 in 650-1000 live births and this prevalence has not decreased over the years, despite an increase in medical terminations (Bittles, Bower, Hussain, & Glasson, 2007; Parker et al., 2010). Down syndrome was named after the nineteenth-century medical doctor John Langdon Down. In his report 'Observations on an Ethnic Classification of Idiots' (1866), Langdon Down addressed their pronounced features, including the characteristic facial appearance, behaviour and distinct cognitive problems (Down, 1866). The most marked cognitive features are the strongly reduced IQ that ranges from 30 to 70 with an

average value of 50 (Vicari, 2004), associated with reduced brain volumes, including hippocampus (Beacher et al., 2010; Pinter et al., 2001; Schmidt-Sidor, Wisniewski, Shepard, & Sersen, 1990), and hippocampal dysfunction, which likely relates to the impairment in verbal short-term memory and hippocampus-mediated explicit long-term memory that are usually present in DS (Lott & Dierssen, 2010; Pennington, Moon, Edgin, Stedron, & Nadel, 2003).

In addition to the congenital intellectual disability, people with DS face accelerated ageing, including early-onset dementia due to Alzheimer's disease (AD) (Zigman, 2013). An estimated 50-70% of DS individuals develop AD by the time they reach 60-70 years of age (Zigman & Lott, 2007). In contrast, AD is present in about 11% of the general population of 65 years and older (Alzheimer's Association, 2015). Although studies have implicated various HSA21 gene products, such as the synapse-associated synaptojanin 1 protein (Arai, Ijuin, Takenawa, Becker, & Takashima, 2002; Cossec et al., 2012; Martin et al., 2014), the strongly increased risk of AD in DS is predominantly attributed to the overexpression of the HSA21-encoded amyloid precursor protein (APP) gene, the precursor of amyloid- $\beta$  (A $\beta$ ), which, in turn, forms the main constituent of the typical AD plaques (Ness et al., 2012). Strikingly, pathological studies revealed that extensive deposition of A $\beta$  plaques, as well as neuroinflammation and substantial numbers of neurofibrillary tangles, are present in virtually all DS individuals aged 40 years and older, twenty to thirty years earlier than in the general population at risk of AD (Mann, Yates, Marcyniuk, & Ravindra, 1986; Mann, 1988; Piessens & Overweg, 1971; Wilcock, 2012; Wisniewski, Wisniewski, & Wen, 1985).

Whereas AD-like neuropathology in DS is thus omnipresent around mid-life, the onset of clinical dementia symptoms is subject to pronounced variation in time and approximately 30-50% of the DS population aged 60-70 years has not developed clinical dementia (reviewed in: Zigman and Lott, 2007). This highly variable time window between the presence of neuropathology and onset of clinical dementia symptoms makes the prediction of the course to dementia a fairly complex endeavour. In addition, the identification of early changes in cognitive functioning is complicated by the (variable degree of) congenital intellectual disability in DS (Devenny, Krinsky-McHale, Sersen, & Silverman, 2000; Oliver, Crayton, Holland, Hall, & Bradbury, 1998; Prasher, 2009). Despite these difficulties, predicting and monitoring the progression of AD dementia in DS is one of the major challenges in clinical practice and of utmost importance to enable adaptive caretaking and therapeutic interventions.

Although auspicious results have been obtained in recent studies on early diagnostic serum biomarkers (Dekker et al., 2015), plasma A $\beta$  (Coppus et al., 2012; Schupf et al., 2010) and telomere shortening (Jenkins et al., 2010, 2012), an established clinical procedure with fairly easy repeatability and limited invasiveness to predict conversion to AD dementia is not yet available. In that respect, behavioural and psychological symptoms of dementia (BPSD) are of great interest, i.e. 'signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia' (Finkel, Costa e Silva, Cohen, Miller, & Sartorius, 1996). BPSD are found in all types of dementia and are among the core symptoms, in addition to cognitive decline and impaired activities of daily living (Finkel et al., 1996; Finkel, 2000). For instance, 80-97% of the AD patients in the general population suffer from one or more BPSD at some point during their disease (Gauthier et al., 2010).

Jost & Grossberg (1996) investigated the temporal relationship between BPSD and the clinical diagnosis of AD and showed that particular BPSD can be acquired before, around or after the AD diagnosis. Social withdrawal, for instance, preceded the clinical diagnosis of AD by an average of 33 months, whilst agitation, aggression and hallucinations were generally observed 1-2 years after AD diagnosis. Recently, we evaluated BPSD in mild cognitive impairment (MCI), i.e. a cognitive state between normal aging and dementia, and found that BPSD were more commonly present in AD than in MCI patients (Van der Mussele et al., 2013b). Three behavioural syndromes were identified in both MCI and AD patients: a depression, an agitation and a psychosis syndrome. Depressive symptoms were most dominant in MCI, whereas AD patients were more subjected to agitation (Van der Mussele, Le Bastard, et al., 2014; Van der Mussele, Mariën, et al., 2014a). The presence of depressive symptoms in MCI was strongly associated with progression to AD in the general population (Van der Mussele, Fransen, et al., 2014).

As such, assessment of BPSD might offer a clinical tool to herald the onset of dementia and monitor its progression in DS as well. Already in 1948, George Jervis, a medical doctor in Thiells (New York), commented on the marked changes in DS subjects with early 'senile' dementia: 'In the few mongoloid idiots who reach the fourth or fifth decade of life, remarkable personality changes may occur, resulting from intellectual and emotional deterioration' (Jervis, 1948). Surprisingly, despite such reports and the high risk to develop AD at a relatively early age in DS, the relationship between AD and behavioural and psychological alterations in this syndrome has been largely neglected so far.

Whereas a substantial amount of studies investigated particular behavioural disturbances in DS, whether or not in relation to the status of dementia, few studies comprehensively assessed BPSD in DS using an integrated approach. Such an approach, i.e. looking at a series of behavioural and psychological changes over time in relation to the onset of clinical dementia symptoms, is essential to improve understanding of the temporal relationship between BPSD and AD in DS. Moreover, accurate identification of BPSD may improve early identification of those at risk, yield novel treatment possibilities and thus improve quality of life, as well as provide a new, non-invasive way to monitor, or at least give an indication of, the complex progression to

dementia in DS. Therefore, this review aims to summarize and evaluate the rather limited knowledge on BPSD in DS and highlight its importance and potential for daily clinical practice.

## **2. Behavioural and psychological symptoms of dementia (BPSD)**

BPSD, or in a narrower sense also known as neuropsychiatric symptoms (NPS), are defined as ‘a heterogeneous range of psychological reactions, psychiatric symptoms and behaviours resulting from the presence of dementia’ (Finkel, 2001; Lyketsos et al., 2011). Even though BPSD have been intensively studied during the last two decades, they are far from being a newly recognized entity. Already in 1906, Alois Alzheimer described hallucinations, delusions, paranoia and agitation in his famous 51-year old patient Auguste Deter, who suffered from a particular form of dementia that later became known as Alzheimer’s disease (Maurer, Volk, & Gerbaldo, 1997).

This heterogeneous group of BPSD is associated with increased suffering, a reduced quality of life, increased risk of mortality, accelerated cognitive decline and earlier institutionalization for patients, severe burden for caregivers and relatives, and increased financial costs (Finkel et al., 1996; Finkel, 2001), and can be assessed and categorized in various ways. More than two dozen scales are available for BPSD in AD and other dementia syndromes in the general population (Finkel, 2000). The most commonly used are the Behavioural Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987; Reisberg, Auer, & Monteiro, 1996) and the Neuropsychiatric Inventory (NPI) (Cummings, 1997; Cummings et al., 1994).

The behavioural and psychological items in the BEHAVE-AD and NPI largely correspond (Table 1) and will be used hereafter to categorize the current knowledge of behavioural changes in DS. The BEHAVE-AD (extensively reviewed in Reisberg et al., 2014) is an informant-based rating scale to assess behavioural disturbances that are related to AD, not including symptoms that primarily relate to functional and cognitive deterioration. It scores 25 behavioural symptoms in seven main symptomatic categories (Table 1) over a two-week interval (Reisberg et al., 1987, 1996). Different versions of the BEHAVE-AD have been established, including a clinician observation-based version to reduce caregiver bias (Auer, Monteiro, & Reisberg, 1996) and a version adapted for institutionalized settings (De Deyn et al., 1999).

The NPI is a validated, structured interview with a caregiver of the patient to assess the frequency and severity of behavioural symptoms over the past month (Cummings et al., 1994). The initial NPI evaluated ten types of neuropsychiatric alterations that are commonly associated with dementia (Table 1). Currently, an extended NPI is used that also includes night-time behaviour disturbances, and appetite and eating abnormalities (Cummings, 1997). Meanwhile, several other forms of the NPI have been created, including a nursing home version (NPI-NH) (Wood et al., 2000), a clinician-rated version (NPI-C) (de Medeiros et al., 2010) and a shortened form, the NPI-Q (questionnaire), for daily clinical use (Kaufer et al., 2000). Whereas the BEHAVE-AD is dedicated to AD, the NPI also includes behavioural symptoms that are rare in AD and more common in other types of dementia (Cummings, 1997).

Strikingly, neither the BEHAVE-AD, nor the NPI, or any other behavioural assessment scales have been adapted and validated for AD in DS, thus not taking the DS-specific circumstances into account, such as preexisting behaviour and limitations associated with intellectual disability. Furthermore, not all items in these scales are equally valuable in DS, e.g. certain behaviour is hardly observed or relatively complex to assess in DS. Therefore, this review aims to take the first step towards a novel scale for BPSD in DS by summarizing and evaluating behavioural studies in DS and by categorizing them according to common classifications of behavioural and psychological symptoms (Table 1). Due to the congenital neurological alterations in DS, it is important to differentiate between changes that are likely related to AD and those behavioural phenotypes that are commonly present among the DS population regardless of AD.

## **3. Diagnosis of BPSD in DS: a challenging endeavour**

Whereas the dementia field largely uses the terminology of BPSD or NPS to address behavioural and psychological changes, reports on demented DS subjects referred to them in numerous ways: from behavioural disturbances (Prasher & Filer, 1995), behavioural changes (Adams et al., 2008; Duggan, Lewis, & Morgan, 1996), behavioural deficits and excesses (Adams & Oliver, 2010; Adams et al., 2008; Millichap et al., 2003) to psychiatric symptoms (Moss & Patel, 1995; Urv, Zigman, & Silverman, 2010), maladaptive behaviour (Cooper & Prasher, 1998; Cosgrave, Tyrrell, McCarron, Gill, & Lawlor, 1999; Urv, Zigman, & Silverman, 2008), challenging behaviour (Huxley, Van-Schaik, & Witts, 2005), behavioural and emotional changes (Temple & Konstantareas, 2005) and personality/behaviour changes (Ball, Holland, Treppner, Watson, & Huppert, 2008; Ball, Holland, Hon, et al., 2006; Holland, Hon, Huppert, & Stevens, 2000; Holland, Hon, Huppert, Stevens, & Watson, 1998), clearly indicating the lack of a consensus approach in the DS field. This diverse terminology will be largely referred to as BPSD in the subsequent sections.

The diagnosis of BPSD is likely different in DS than in the general population. Such diagnoses in people with intellectual disabilities, including DS, are complicated by various problems (reviewed in: Bouras and Holt, 2007). Importantly, intellectually disabled persons, and especially those with more severe disability, have an apparent difficulty to verbalize their emotions (Moss et al., 1993), causing the diagnosis to primarily rely on clinically observable behaviour and information from key informants (Moss et al., 1993; Smiley & Cooper, 2003). For instance, understanding of relatively complex concepts, such as worthlessness or guilt, has been reported to require a developmental level of at least seven years of age. As such, many people with moderate to severe intellectual disability, including many individuals with DS, will have no, or only a scanty, notion of

such concepts. Therefore, the diagnosis of depression, for example, cannot rely solely on patient interviews as feelings indicating depression may not be verbally expressed (Adams et al., 2008; Smiley & Cooper, 2003). Accordingly, referral is most often initiated by caregivers (Bouras & Holt, 2007). So far, the diagnosis of BPSD in DS has predominantly relied on informant interviews with the main caregivers and/or relatives. Studies based on such interviews have suggested that the behavioural presentation of AD in DS is different from that in the general population. In particular, BPSD appear to be more prominent than, and present prior to, the decline in episodic memory (Ball et al., 2008; Ball, Holland, Hon, et al., 2006; Nelson, Orme, Osann, & Lott, 2001). There may be several reasons for this, e.g. informants may be more sensitive to particular changes in behaviour and personality, especially those affecting daily care and management, as compared to cognitive changes. Consequently, this would lead to relative over-reporting of (certain) BPSD as compared to the deterioration in memory functioning (Adams et al., 2008; Holland et al., 1998). Moreover, the presence of any (peripheral) disorder should be carefully assessed to prevent interpretation of related behavioural changes as dementia (Prasher, 2009). Conversely, underreporting of symptoms is common too, e.g. due to frequent changes of professional caregivers, denial or misinterpretation of AD symptoms as normal ageing. Informants are generally able to observe the onset of certain BPSD that were not, or rarely, observed in the patient before, whereas it is rather hard to note mild- to moderate behavioural alterations if the specific behaviour is already frequently, and often variably, present. Although caregiver reports are often reliable (Jamieson-Craig, Scior, Chan, Fenton, & Strydom, 2010), they may sometimes be biased and confounded by various factors. As such, clinicians cannot always fully rely on this information (Auer et al., 1996).

In addition, Capone, Goyal, Ares, & Lannigan (2006) stressed the complex distinction between learned behaviour and psychiatric symptoms in people with limited skills, such as those with DS. It is important to distinguish psychiatric symptomatology from the overall picture of problem behaviour, as this allows for specific and realistic behavioural, educational and pharmacological interventions. For instance, Fenner, Hewitt, & Torpy (1987) reported particularly marked inactivity and strange habits in DS, which remained relatively constant with age. However, this behaviour was not likely related to DS, but rather a consequence of prolonged hospitalization, causing such reports to be of limited value. This demonstrates the importance of considering the individual circumstances of the patient when evaluating BPSD, including their living situation, i.e. in community dwellings, assisted living facilities or larger institutionalized settings, such as nursing homes or hospitals. Although certain behaviour likely relates to the institutionalized environment (Fenner et al., 1987; Linaker & Nitter, 1990), a higher frequency of delusions, hallucinations, anxiety and aggressiveness has been reported in memory clinic outpatients with AD in the general population compared to their institutionalized counterparts (Cheng et al., 2009). This may relate to higher stress of family caregivers of community dwelling patients compared to care provided by professional caregivers in institutions, positive effects of specialized institutionalized care, and/or a higher use of psychotropic medication in institutions. In turn, BPSD are a major cause for early institutionalization (Finkel, 2000).

Since no specific scale to assess BPSD in DS is yet available, particular BPSD items in DS are mainly assessed using certain sub-scales or domains of existing questionnaires that assess dementia in DS. The choice for a particular scale used in daily clinical practice is based on numerous factors, including the historical use of a certain questionnaire in a clinic or institute, personal preference of clinicians and caregivers, available time, country of origin and presence of a scale in the native language. However, the use of only one scale does not likely yield enough information to properly assess BPSD: certain BPSD items are extractable from individual dementia scales, but none of the existing ones have an all-embracing approach like the BEHAVE-AD or NPI. As a consequence, the limited number of BPSD studies in DS were nearly all conducted with different, sub-optimal scales (Table 2 and 3). Cross-sectional and longitudinal BPSD studies in the demented DS population are discussed in section 4, followed by section 5 that focuses on individual behavioural and psychological symptoms regardless of dementia (Table 4). More specifically, section 5 presents items that are (generally) present in a non-demented DS population, which may complicate the BPSD diagnosis, and should thus be cautiously considered with regard to a novel BPSD scale for AD in DS.

Due to the relatively limited number of studies on BPSD in DS, we applied a broad, unrestricted search strategy to identify as many relevant papers as possible. PubMed and EBSCO Host Academic Search Premier databases were searched, as well as authors' own archives of articles. Initial selection of papers was based on the relevance of titles and abstracts. Non-English articles, case study reports and paediatric DS studies were not taken into consideration in this review.

## **4. BPSD studies in DS**

### **4.1. Cross-sectional approaches**

The first paper to report on BPSD in a series of demented DS individuals was published by Dalton and Crapper-McLachlan (1986). They summarized a total of 35 reported cases (63% female) that were described between 1946 and 1985. Neuropathological confirmation of AD was available in 33 cases. Clinical dementia was present in 25 individuals. Common reported features were personality changes and apathy/inactivity (Table 2), while depression, disorientation and hallucinations/delusions were less prevalent. Subsequently, Lai & Williams (1989) evaluated 96 DS subjects, of which 49 were clinically demented. Based on clinical observations and caregiver interviews, they reported that memory disturbances, an early sign of AD in the general population, were only noted in a few participants, whilst personality changes, like

irritability and emotional lability, were primarily observed as the initial presentations of AD (Table 2). Subjects with more severe intellectual disability also required assistance with daily tasks and presented apathy, inattention and decreased social interactions as earliest signs of dementia.

Resembling the cohort of Lai & Williams, i.e. primarily institutionalized and a minority living in community-based group homes, Haveman et al. (1994) studied 201 persons with DS living in institutions and 106 in group homes. DS individuals with mild and severe disability presented more psychological problems with ageing. In particular, they displayed more incoherent behaviour, apathy, drowsiness, irritation, fear, feeling sad, lack of appetite, night-time restlessness and suspiciousness with advancing age than intellectually disabled individuals of another aetiology (Table 2). Taking the presence of dementia into account, the authors concluded that these psychological aberrations could be largely explained as primary and secondary symptoms of dementia, also after correcting for age, gender and the level of intellectual disability (Haveman et al., 1994). Using questionnaire-based caregiver interviews, Prasher & Filer (1995) studied 25 non-demented and 15 demented DS individuals and found that demented subjects displayed significantly increased difficulties with activities of daily living, tiredness, day-time wandering and sleep disturbances (Table 2). Lower mood was also significantly more often observed among the demented group (although two participants treated for concurrent depressive episodes were excluded). No changes were reported for aggression, restlessness, nighttime wandering and eating disturbances (Prasher & Filer, 1995).

In the subsequent years, two studies were published regarding BPSD in people with intellectual disabilities, of which small subgroups consisted of DS participants (Table 2). Firstly, Moss & Patel (1995) investigated psychiatric symptoms in 99 intellectually disabled patients: twelve demented subjects (five DS) were compared to 87 non-demented individuals (four DS). Informant-interviews revealed that demented subjects presented an increased loss of interest, irritability, slowness, and sleep difficulties, whilst depressed mood and delayed sleep were less common, compared to those without dementia. Deduction of DS-specific results was impossible due to a low number of DS subjects and data pooling of all participants.

Similarly, Duggan et al. (1996) evaluated twelve people with mild to moderate intellectual disabilities and dementia, eight of which had DS. The behavioural history was assessed in relation to the duration of dementia, being the first paper to enlighten temporal relationships between BPSD and dementia. In contrast to the study of Moss and Patel, this study reported the behavioural history per subject, allowing an indicative exploration of DS-specific behavioural changes in dementia. Among the DS group, multiple individuals presented with particular BPSD symptoms, i.e. aggression (6/8), delusions (3/8), depression (3/8) and hallucinations (4/8). Altered eating behaviour (3/8 DS subjects left food unswallowed in their mouths) were reported as well. In addition, diurnal rhythm disturbances and incontinence and misplacement of objects were observed, although it was not noted how many DS individuals presented this behaviour (Duggan et al., 1996).

Two years later, a slightly more extensive study assessed behavioural and psychological symptoms in nineteen demented DS subjects compared to demented persons with intellectual disabilities of other aetiologies (on average twenty years older than those with DS). Disturbed sleep, restlessness and low mood were more prevalent in the DS group, whilst aggression was more frequently observed in those with a non-DS intellectual disability (Table 2). Even though not significant, the authors also reported increased uncooperativeness, auditory hallucinations and lack of energy in the DS group (Cooper & Prasher, 1998).

Although these seven studies provide preliminary insights into BPSD in DS, a universal picture cannot be drawn due to various major limitations. Firstly, among the rather small number of (often institutionalized) participants, females were generally overrepresented. Gender may influence the prevalence of certain BPSD, e.g. depression is more prevalent in females, both in the general population and in DS (Cooper & Collacott, 1994; Walker, Dosen, Buitelaar, & Janzing, 2011). Secondly, participants were relatively old (mean age >50 years), thus likely missing early BPSD symptoms that may predict the development of AD dementia in DS. Thirdly, studies were retrospective and the dementia severity was not considered in the analyses, thus not identifying the temporal relationship between behavioural problems and the progression of dementia.

The first longitudinal approach was undertaken by Holland and co-workers (further discussed in section 4.2). In their cross-sectional baseline study (Table 2), eighteen out of 75 DS subjects were diagnosed with dementia, of whom thirteen (72.2%) presented behaviour and personality changes. Apathy/lack of motivation was markedly present in ten (55.6%) of the demented individuals, compared to 15.8% in the nondemented group. Though no statistics were applied, apathy appeared to be more common in the demented subjects (Holland et al., 2000, 1998).

In agreement, Huxley et al. (2005) found that the frequency and severity of lethargy and hyperactivity was significantly higher in demented than in non-demented DS subjects. Similar results, close to significance, were reported for irritability and stereotypy. Although the two groups differed significantly in age (Table 2), age was not significantly correlated with the behavioural outcome measures. Therefore, the authors concluded that these behavioural alterations are associated with dementia rather than normal ageing.

Apathy was also assessed by Temple & Konstantareas (2005). They assessed BPSD in DS using the BEHAVE-AD (Table 1), together with the apathy subscale of the CERAD Behavioural Rating Scale for Dementia that compensates for the lack of a measure for apathy in the BEHAVE-AD. AD patients with DS (DS-AD, n=30, average age of 52 years) and without DS (AD-only, n=30, average age of 80 years) were evaluated by completion of both scales by a primary caregiver and by direct clinical observations during day-care

programmes. Based on the BEHAVE-AD/CERAD scores, it was reported that the DS-AD group presented significantly more activity disturbances and less delusions and hallucinations. In agreement, day-care program observations revealed significantly increased purposeful and non-purposeful motor behaviour in DS-AD, as well as decreased mood (Table 2).

Using the Behavioural and Emotional Activities Manifested in Dementia (Beam-D) scale, which is used for BPSD in the general population, Jozsvai (2006) assessed nineteen demented individuals with DS and compared his findings to those in a 'normative' demented population without intellectual disability (more than twenty years older than those with DS). Non-compliance, i.e. the extent to which subjects follow demands, instructions and directions from a caregiver, occurred with higher frequency and severity in the demented DS persons compared to the normative group (Table 2). The wilful destruction of property was rated more severe in the DS group as well. In contrast, insomnia was significantly more severe in the normative group.

Deb et al. (2007) undertook a different approach, neither using clinical assessments nor established questionnaires, but fully relying on caregivers' perception and description of behavioural changes that might be associated with development of AD in DS. The most noticeable early signs of AD were forgetfulness and confusion. Moreover, a general slowness was observed in various aspects of daily functioning (eating, speaking, walking), as well as loss of interest and motivation, social withdrawal, sleep problems and emotional changes (tearfulness, being upset). These observations point in the direction of activity, affective and diurnal rhythm disturbances in terms of BPSD categories.

These studies did not consider prodromal stages of dementia prior to clinical dementia diagnosis. Urv and co-workers associated the presence of maladaptive behaviour with the status of dementia, i.e. no dementia, questionable dementia (which largely resembles MCI in the general population), possible dementia and definite dementia. The non-demented group presented the lowest frequency and severity of maladaptive behaviour. To reveal possible early signs of AD in DS, the groups with no dementia and questionable dementia were compared and it was reported that a higher number of questionable-demented subjects presented regressive behaviour, inattentiveness, low energy, non-assertiveness, withdrawal, destructiveness, hostility, impulsivity, object attachment and aggressive behaviour (Table 2). Furthermore, confused thinking and tiredness were significantly more common in possible-demented than in non-demented individuals. Overall, those with questionable, possible and definite dementia presented more physical symptoms of depression, e.g. low energy, than those without dementia. Finally, dependence, fearfulness, low energy, nonassertiveness, sadness, self-injurious behaviour, self-stimulation, sleep problems, unusual motor behaviour and withdrawal were most common in the definite demented group, whereas this group displayed the lowest prevalence of aggressiveness, attention-seeking, being overly sensitive, complaining, destructiveness, eating, impulsivity, overactivity, paranoia, social inadequacies and tantrums (Urv et al., 2008).

Two years later, this cohort was re-assessed using this four-part dementia classification, now in relation to psychiatric symptoms. Similarly, the non-demented group presented the lowest frequency of psychiatric symptoms, i.e. delusions, hallucinations, behavioural disturbances and depression. Interestingly, the proportion of subjects presenting delusions, depressive symptoms (non-event related sadness, sleeping difficulties and eating disturbances) and wandering were the lowest in the non-demented group and increased with the status of dementia to the highest proportion in the definite dementia group. Again, to reveal early signs of AD in DS, the non-demented and questionable-demented groups were compared: those with questionable dementia were twice as likely to display paranoid ideation of things being stolen, 2.6 times more likely to present verbal and physical violence and showed a higher prevalence non-event related sadness, eating problems and sleeping difficulties. In addition, agitation/restlessness, threatening behaviour and wandering were most frequent in those with definite dementia (Urv et al., 2010). In agreement, Oliver and coworkers (2011) demonstrated that behavioural excesses (pooled scores from eleven items) and deficits (pooled scores from seventeen items) were significantly more common in demented DS individuals (n=12) with regard to their number, frequency and management (Oliver, Kalsy, Mcquillan, & Hall, 2011). In short, particular psychiatric symptoms seem to correlate with the status of dementia and might thus facilitate earlier diagnosis of AD in DS.

Recently, we examined BPSD in relation to the status of dementia by studying demented, converted and non-demented DS subjects and its possible neurobiological underpinnings (Dekker et al., 2015). In a longitudinal clinical follow-up of 10-14 years, 151 DS participants were yearly assessed using two validated functional scales, i.e. the Dementia Questionnaire for persons with an intellectual disability (DMR) (Evenhuis, Kengen, & Eurlings, 1998) and Social Competence Rating Scale for persons with an intellectual disability (SRZ) (Kraijer, Kema, & de Bildt, 2004). The DMR and SRZ were not specifically developed for evaluating BPSD, but report on short- and long-term memory, social functioning and activities of daily living. Consequently, we selected questions from the scales that mapped onto a category of the BEHAVE-AD rating scale, which enabled us to extract four out of seven BEHAVE-AD items, i.e. paranoid and delusional ideation, affective disturbances, aggressiveness and diurnal rhythm disturbances. Based on certain questions from the DMR and SRZ, we reported that diurnal rhythm disturbances, apathy and aggressiveness were significantly more frequent in the demented group compared to the converted and non-demented subjects (Dekker et al., 2015).

Taken together, mounting evidence suggests that particular BPSD are generally more prevalent in DS individuals diagnosed with dementia compared to those without. Only Cosgrave et al. (1999) reported no

increased prevalence of behavioural disturbances in demented DS individuals. More than a dozen cross-sectional studies have been published using a variety of measures for dementia symptoms, but none took a comprehensive approach to assess all BPSD items in DS. This is likely related to the use of various, quite diverse, suboptimal scales from which particular BPSD items were extracted. The lack of a validated BPSD scale for DS, like the BEHAVE-AD and NPI in the general AD population, together with the relatively limited group sizes do not enable reasonable inter-study comparisons. Comparisons with diverse control groups were used: from non-demented persons with DS or individuals with intellectual disabilities of other aetiologies to AD patients in the general population. Finally, a temporal relationship between BPSD and the onset and progression of dementia cannot be established from these cross-sectional approaches, pointing at the great exigency for longitudinal approaches.

#### 4.2. Longitudinal approaches

In DS individuals, AD-like neuropathology is extensively present from 40 years of age. The onset of clinical dementia symptoms, however, tremendously varies in time. Hence, a cross-sectional study design including clinically demented and non-demented DS groups is rather restrictive: progressive neurobiological changes in the DS brain likely affect behaviour already long before memory decline is observed (Dekker et al., 2015). In addition, the previously discussed studies primarily comprised elderly cohorts (mean age of 50 years and older), therefore likely presenting extensive AD-like neuropathology. Accordingly, early BPSD that correlate with the advancing neuropathology are likely missed, pointing at the need for longitudinal assessments that start at a younger age. Table 3 enlists longitudinal studies that (partially) assessed BPSD in DS.

To our knowledge, Evenhuis (1990) initiated the first longitudinal approach. The clinical course of dementia was prospectively assessed for seventeen middle-aged DS individuals. Standardized diagnostic procedures for dementia in DS were not available at the time, and the author relied on careful sequential clinical observations, medical examinations, history taking, and, if institutionalized, interviews with nurses at least twice a year. Fourteen out of seventeen subjects developed dementia that was neuropathologically confirmed as AD. Interestingly, apathy and withdrawal, as well as daytime sleepiness, were markedly reported in the first year of dementia, which was the first indication of (relatively) early signs of dementia in DS (Evenhuis, 1990).

In the same decade, Visser et al. (1997) followed 307 institutionalized DS subjects for five to ten years to assess dementia and other clinical symptoms. Using a self-developed Early Signs of Dementia Checklist, decreased interest, motivation and general pace, as well as mood changes and exaggeration of personality traits, were found among the first signs of deterioration. With the onset of distinctive dementia (56 subjects developed dementia), these signs increased in prevalence. Furthermore, temporal and spatial disorientation, nocturnal anxiety and reversal of diurnal rhythm were more pronounced in demented individuals. Aware of the institutionalized setting, this study suggested, again, that apathy is an early dementia symptom in DS. A more encompassing longitudinal study was undertaken by Holland and co-workers (Table 3).

Changes in four domains, i.e. personality/behaviour, memory, daily living skills and general mental functioning, were assessed at baseline (n=75 DS) and re-assessed after clinical follow-ups of eighteen months (n=68) and five years (n=55). Interestingly, the first and primary alterations over the first eighteen months concerned BPSD rather than memory. Indeed, in the age groups of 30-39 and 40-49 years of age, 29.2% and 31% (respectively) presented changes in personality, without changes in memory and/or the other two domains. In retrospect, relatives and caregivers particularly noted changes in apathy and stubbornness, which are more typical frontal lobe symptoms. Therefore, the authors suggested that such frontal lobe-related changes in behaviour and personality, rather than cognitive decline, might be the earliest sign of AD in DS and, as such, predict the onset of AD (Holland et al., 2000, 1998).

In continuation, 55 participants from this cohort were followed for five years, specifically assessing early BPSD in relation to diagnostic criteria for frontotemporal dementia (FTD) (Ball, Holland, Hon, et al., 2006). Four DS subjects had AD at baseline, another six developed AD over the course of five years. Importantly, among these six converters, four met criteria for FTD at baseline. Ball and co-workers reported that meeting the FTD criteria conveyed at least a 1.5 times higher chance to develop AD over five years. Furthermore, the presence of at least one change in behaviour and personality (not yet sufficient to establish the FTD diagnosis) yielded at least a 1.5 times higher risk to develop FTD-like symptoms, memory changes or AD over the course of five years in DS subjects that had no memory changes or dementia at baseline. In other words, altered behaviour and personality appeared to be an early and predictive sign of AD in DS. Interestingly, whereas MCI is known to convey a strongly elevated risk to develop AD in the general population (Jessen et al., 2014), memory changes in DS individuals did not significantly increase the odds to convert to AD over the five year period (Ball, Holland, Hon, et al., 2006). The authors therefore suggested that AD in DS is initially revealed as frontal lobe-associated behaviour and personality changes without prominent functional memory decline. Conversely, Adams & Oliver (2010) reported an increased frequency of BPSD only in DS individuals with cognitive deterioration. They followed thirty DS individuals for a period of sixteen months. Based on the Neuropsychological Assessment of Dementia in Individuals with Intellectual Disabilities test battery, ten individuals were identified with early cognitive deterioration over this period. Only in those with cognitive deterioration, a significantly increased frequency of behavioural excesses and deficits (not specified) was

observed. In agreement, other (cross-sectional) studies previously reported deteriorated episodic memory prior to the full clinical diagnosis of AD in DS (Deb et al., 2007; Devenny et al., 2000; Devenny, Zimmerli, Kittler, & Krinsky-McHale, 2002; Krinsky-McHale, Devenny, & Silverman, 2002). Caregivers of demented DS subjects described confusion and general forgetfulness with a particular loss of recent memories and relative spared distant memory as the most prominent early sign of dementia in DS (Deb et al., 2007). Depending on the particular tests and the study population, it might therefore be more likely that changes in behaviour and personality do not only precede, but are also accompanied by cognitive decline prior to the AD diagnosis. In addition, the FTD diagnosis of DS subjects should be attenuated. FTD is clinically manifested in two subtypes: primary progressive aphasia and the behavioural variant of frontotemporal dementia (bvFTD). Indeed, the bvFTD comprises severe behaviour and personality changes, including apathy, disinhibition, executive dysfunction, loss of empathy or stereotypic behaviour, with relative preservation of memory (Sieben et al., 2012). Differential diagnosis between bvFTD and AD, specifically the frontal variant of AD with prominent behavioural aberrations and executive dysfunction, is fairly difficult when solely based on clinical data (Woodward et al., 2010). Ball and co-workers utilized the rather broad clinical criteria of the FTD checklist by Gregory and Hodges (1993). However, the neuropathology underlying FTD is different from AD, and to the best of our knowledge, FTD-positive neuroimaging or neuropathology in demented DS subjects has not been demonstrated so far. Therefore, the reported cases of FTD in DS are most probably cases of AD with prominent frontal features (frontal variant), which would be most in line with the AD-like neuropathology in DS. Instead of FTD, or FTD-like symptoms, we will thus refer to frontal lobe symptoms in the remainder of this review. To more extensively assess the hypothesized frontal lobe dysfunction, executive function (generally associated with frontal lobe integrity) was studied in 122 DS subjects, including the aforementioned 55 subjects (Ball et al., 2008). Again, a substantial percentage of non-demented participants (60.3%) presented one or more changes in behaviour/personality, of which a subgroup (29.8%) also showed memory changes. Particularly marked were reduced empathy (43.6%), emotional lability (35.9%), social withdrawal (21.8%), distractibility (16.7%), perseveration/verbal stereotypes/echolalia (16.7%), disinhibition (14.1%), impulsivity (14.1%) and apathy (14.1%). Notably, the number of informant-reported BPSD in the non-demented DS group significantly predicted the performance on two (frontal-lobe associated) executive function tasks (Tower of London, scrambled boxes), which supported the authors' hypothesis that behaviour/personality alterations and executive dysfunction, associated with frontal lobe dysfunction, are early signs of AD in DS (Ball et al., 2008).

Supportive evidence of this hypothesis was generated by two other studies. In a cross-sectional approach, Deb et al. (2007) reported the early presence of marked forgetfulness, as well as frontal lobe-related symptoms, i.e. lack of interest and motivation, social withdrawal, depressive symptoms and general pervasive slowness (section 4, Table 2). Secondly, Nelson and co-workers, showed that individuals with abnormal physical findings at baseline (atrophy and ventricular enlargement on MRI and pathological reflexes during neurological examination) scored significantly lower on cognitive functioning, including memory (indicative of probable dementia), and higher on indifference and depression, both at baseline and after follow-up of one year. Indeed, indifference and depression are associated with prefrontal lobe dysfunction (Nelson et al., 2001).

Despite the various indications in favour of an early frontal lobe dysfunction hypothesis in DS, these frontal lobe symptoms may not be as informative as has been suggested. Recently, we found that at least one frontal lobe symptom of the Middelheim Frontality Scale, which discriminates between AD and FTD (De Deyn et al., 2005a), was displayed in 84% of the MCI patients and 97% of the AD patients in the general population, but also in 50% of the control group (Van der Musselle et al., 2013b). Therefore, it is essential not to overestimate the importance of frontal lobe symptoms and continue investigating the full range of BPSD in DS. Urv et al. (2008), for instance, compared maladaptive behaviour in non-demented DS individuals that remained non-demented to those that converted to questionable dementia (largely resembling MCI), thus pointing at early dementia symptoms (Table 3). A range of BPSD items, not only frontal lobe symptoms, were significantly more prevalent in the converters: confused thinking, dependence, fearfulness, object attachment, regressive behaviour, sadness and social inadequacies (Urv et al., 2008).

In summary, not more than a mere handful of studies longitudinally assessed BPSD in DS. Although these studies provided the first insights into the relationship between BPSD and dementia in DS, new prospective studies are needed to further elucidate the temporal relationship. It is especially worth considering which subjects constitute the control group. After all, non-demented DS subjects of 40 years and older do not have clinical dementia symptoms but are in neuropathological terms AD-positive. Furthermore, the suggestion that frontal lobe symptoms are an early indicator of AD is of great interest, but it should be taken into account that these results were obtained in a relatively small cohort that presumably had established AD-like neuropathology. Therefore, future investigations should also include younger DS adults and assess the multitude of BPSD rather than only frontal lobe-associated behaviour and personality changes.

## **5. Behavioural and psychological phenotypes in DS**

Since Langdon Down's 'Observations on an Ethnic Classification of Idiots' (1866) and Mitchell's notes on sixty-two cases of 'kalmuc idiots' (1876), clinicians and researchers have tried to describe and define a typical behavioural phenotype of DS (Collacott, Cooper, Branford, & McGrother, 1998; Down, 1866; Fraser &



Mitchell, 1876). Is there indeed a characteristic behavioural phenotype of DS, and if so, which recurrent symptoms are generally present? Such pre-morbid symptoms are particularly relevant to take into account when assessing BPSD in DS. After all, the onset of a particular BPSD that was not, or hardly, observed in the patient is more likely noticed than alterations in frequency and/or severity of behaviour that was already commonly, and presumably also variably, present. To understand behavioural and psychological changes in DS, it is thus essential to evaluate behaviour not only during, but also (long) before the onset of the clinical dementia symptoms. Section 5 discusses such behavioural and psychological changes in DS regardless of dementia.

One of the first comprehensive studies to examine a behavioural phenotype in DS adults was published by Collacott et al. (1998). In a large, population-based study, thirteen maladaptive behaviours were assessed in 360 adults with DS and 1829 adults with intellectual disabilities of other aetiologies (Table 4). Absconsion, aggression, antisocial behaviour, attention-seeking, excessive activity, making excessive noise, disturbing others at night, property destruction, scattering objects, self-injury, and untruthfulness were significantly less prevalent in DS individuals compared to those with intellectual disabilities of other aetiologies, pointing at a specific behavioural phenotype of DS. Regarding the early presence of AD neuropathology in DS, the study population was subsequently subdivided into a group younger than 35 years of age and a group of 35 years and older. No significant differences were revealed between both groups, likely due to the fact that behaviour was scored on a dichotomous scale (present/absent) (Collacott et al., 1998). For instance, behaviour that increased from 'sometimes' to 'often' would be rated similarly using such a binominal scoring, thus omitting any information about severity and frequency.

Similarly, Straccia, Baggio & Barisnikov (2014) compared 34 non-demented DS subjects to 34 intellectually disabled persons of other aetiology. The DS group scored significantly lower on mental illnesses, especially on subscales for avoidant disorder, psychosis and behavioural signs of depression. In addition, lower scores for behavioural problems were reported in the DS group, in particular for aggressive/disruptive, self-absorbed and depressive behaviour. Conversely, the DS group scored significantly higher on general social behaviour, social attitude, socio-emotional behaviour and respect of social rules.

Compared to the general population, however, a higher prevalence of behavioural disturbances seems to be present in DS. Indeed, it has been estimated that psychiatric co-morbidity is prevalent in 18-38% of the DS children, which is greater than in the general population, but probably lower than in other intellectual disabilities (Capone et al., 2006). Problem behaviour was also more commonly reported in late adolescents with DS than in those without DS (van Gameren-Oosterom et al., 2013). Higher scores, indicating more problem behaviour, were observed in those with more severe intellectual disability. The largest differences were observed for withdrawal, somatic complaints, social problems, attention problems and thought problems. Compared to typical behaviour in DS children (not further discussed in this article and reviewed by Capone et al. (2006), Dykens (2007), Visootsak and Sherman (2007)), a decrease in externalizing behaviour (aggression, inattention, hyperactivity, opposition) and an increase in internalizing behaviour (withdrawal, shyness, depression) has been observed with ageing to adolescence and adulthood (Capone et al., 2006; Dykens, 2007; van Gameren-Oosterom et al., 2013; Visootsak & Sherman, 2007). However, in a cross-sectional (n=25) and a longitudinal (n=28) cohort of non-demented adults with DS, no significant associations were reported between age and the number and severity of behavioural and emotional problems, taking gender, medical co-morbidities and the level of intellectual disability into account as covariates (Makary et al., 2014).

Despite the use of a large variety of (sub-optimal) scales and diverging study results, particular behaviours appear to be more prevalent in DS than in the general population. In addition to the previously discussed cross-sectional (Table 2) and longitudinal dementia studies (Table 3), section 5 describes behavioural and psychological changes in DS regardless of dementia, classified according to the items of the BEHAVE-AD (Table 1). Section 5 very briefly recapitulates the results from the dementia studies, followed by a discussion of studies that did not consider dementia in DS (Table 4), which is important for establishing whether particular behaviour is omnipresent in adult DS individuals or whether the that behaviour primarily relates to the onset and progression of dementia. In summary, Figure 1 depicts the temporal relationship between BPSD and the clinical diagnosis of AD. Cautious interpretation is required, however, as longitudinal studies assessing the temporal relationship between BPSD and the status of dementia are largely lacking.

### *5.1. Activity disturbances*

Activity disturbances are among the most common and relatively persistent BPSD in the general AD population, with a reported point prevalence up to 58% (Cheng et al., 2009; Eustace et al., 2002). Mounting evidence suggests that activity disturbances are also significantly more prevalent in demented DS subjects than in AD patients without DS (Temple & Konstantareas, 2005) or demented individuals with intellectual disability of another aetiology (Cooper & Prasher, 1998). In addition, Huxley et al. (2005) found an increased frequency and severity of hyperactive behaviour in DS individuals with (early) dementia, compared to a nondemented DS group. Conversely, a study based on caregivers' reports revealed that a general slowness of daily functioning was markedly noted in demented DS individuals (Deb et al., 2007), which corresponds to the observations of Moss & Patel (1995) in a group of demented intellectually disabled persons.

Whilst such inconsistent results have been reported in the demented DS population, those without

clinical dementia symptoms provide a more clear-cut picture. As discussed above, a decrease in externalizing behaviour, including hyperactivity, has been associated with ageing in DS. Relatively high scores of hyperactivity/attention problems were found in DS children with a reported prevalence of ADHD up to 43.9% (Ekstein, Glick, Weill, Kay, & Berger, 2011), as well as in adolescents with DS, and this strongly decreased towards adulthood (Capone et al., 2006; Dykens, 2007; van Gasteren-Oosterom et al., 2013). Indeed, significantly less excessive activity was reported in DS than in intellectual disabilities of other aetiologies (Collacott et al., 1998). Charlot, Fox & Friedlander (2002) reported (obsessional) slowness in eleven DS adults of 21-45 years of age. Furthermore, reduced activity may relate to the high prevalence of obesity that has been reported in the DS population (Melville, Cooper, McGrother, Thorp, & Collacott, 2005; Prasher, 1995b; Rubin, Rimmer, Chicoine, Braddock, & McGuire, 1998).

In sum, hyperactivity in DS probably diminishes with increasing age. The onset of dementia in DS seems to be marked by either a general slowness or by excessive activity. It is speculative whether this relates to different subpopulations or a different status of dementia, and should be investigated further.

Nevertheless, activity disturbances are generally easy to observe for non-clinicians and are thus likely to be noted as BPSD by caregivers and relatives. Elucidating the progression of activity disturbances in relation to dementia in DS is of essence as detection of activity alterations may constitute a clearly observable indication for referral.

## *5.2. Affective disturbances*

The relationship between apathy and depression is complex and it has long been disputed whether apathy should be considered as a separate neuropsychiatric item. Although apathy is clearly related to depression, nearly half of the AD patients presenting apathy do not have major depression, i.e. loss of interest is more common than depressed mood, thus settling this controversy in favour of apathy as a separate item (Landes, Sperry, & Strauss, 2005; Mortby, Maercker, & Forstmeier, 2012; Tagariello, Girardi, & Amore, 2009). Apathy is generally defined as a loss of motivation and is, among other symptoms, particularly manifested by diminished interest, indifference, and blunted emotional responses. Besides the commonalities between apathy and depression, depression also comprises guilt, pessimism and self-criticism, such as feelings of worthlessness (Landes et al., 2005; Marin, 1996; Tagariello et al., 2009). Nevertheless, the overlap between apathy and depression, together with the use of different definitions and scales, cause large variation in the prevalence reports of apathy in the AD population (Tagariello et al., 2009). Indeed, apathy is often misdiagnosed as depression, even if signs of dysphoria or depressed mood are absent (Mortby et al., 2012). For effective treatment, however, careful identification of the symptoms is required to accurately distinguish between apathy and depression. It has been suggested that feelings of worthlessness, for instance, could be helpful for the differential diagnosis (Tagariello et al., 2009). As previously discussed, DS individuals have marked difficulty to express their feelings, thus complicating the differential diagnosis. Taking this into account, the hereafter discussed studies into apathy and depression in DS should be cautiously interpreted.

### *5.2.1. Apathy and isolation*

Apathy is the most common BPSD in the general AD population with a reported prevalence up to 77% (Mega, Cummings, Fiorello, & Gornbein, 1996; Mitchell, Herrmann, & Lanctôt, 2011). An increasing body of evidence also suggests that apathy is common in demented DS individuals (Deb et al., 2007; Dekker et al., 2015; Evenhuis, 1990; Haveman et al., 1994; Holland et al., 2000, 1998; Lai & Williams, 1989; Moss & Patel, 1995; Nelson et al., 2001; Oliver & Holland, 1986; Visser et al., 1997). However, apathy is frequently observed in non-demented DS subjects as well. In a relatively young group of hospitalized DS subjects, Fenner et al. (1987) reported withdrawal and inactivity, both associated with apathy, in respectively 18% and 39% of the individuals (Table 4), although this high prevalence is likely due to their hospitalization. Next, in a cohort of 529 individuals with intellectual disability (202 DS), it was found that withdrawal and emotional instability (e.g. mood changes) coincided with significant regression in adaptive behaviour (Urv, Zigman, & Silverman, 2003). Furthermore, in two population-based samples (Table 2 and 3) apathy was reported in resp. 18% and 14.1% and social withdrawal in 16% and 21.8% of the non-demented DS individuals (Ball et al., 2008; Ball, Holland, Hon, et al., 2006). In continuation, Ball et al. more extensively studied apathetic features in relation to their hypothesis of frontal lobe-associated alterations as early sign of AD in DS. Based on informant interviews with the main caregiver of 78 non-demented DS adults, 47 non-demented individuals exhibited one or more frontal-lobe symptoms. Among those 47 subjects, 27 (57.4%) presented apathetic features (Ball, Holland, Watson, & Huppert, 2010). Similarly, Ghezzi and co-workers (2014) reported increased loss of interest, social isolation in non-demented DS individuals over forty years of age, which likely relates to the AD-like neuropathology that is present at that age. Therefore, apathy is apparently omnipresent and, as such, an important (early) BPSD item to identify in DS.

This is particularly relevant as apathetic individuals generally show impairment in daily living skills, and apathy, as such, could lead to activity disturbances. Indeed, increased fatigue in daily tasks was reported in older, non-demented DS adults (Ghezzi et al., 2014). The lack of identification of apathetic behaviour might cause caregivers to misinterpret the symptoms as deliberate opposition or laziness (Landes et al., 2005). Indeed, caregivers of demented DS subjects noted a pronounced lack of interest and motivation and related behaviour, and reported this as laziness (Deb et al., 2007). Together with the lack of accurate differential diagnosis in various studies, this demonstrates the need for a novel BPSD scale in DS, which should include

clear measures to distinguish between apathy and depression.

### 5.2.2. Depression

The abovementioned studies (section 4, Tables 2 and 3) suggested that demented DS subjects have an increased prevalence of low mood (Cooper & Prasher, 1998; Nelson et al., 2001; Prasher & Filer, 1995; Temple & Konstantareas, 2005). The association between dementia and depression was confirmed in 61 persons with DS: all DS subjects with functional decline were depressed, and 43% of the depressed DS subjects had functional decline compared to none of the depressed individuals with intellectual disabilities of other aetiologies (Burt, Loveland, & Lewis, 1992). Specifically, depressive symptomatology associated with dementia in DS included depressed mood, reduced appetite, weight loss, slowing and disturbed sleep patterns (Prasher, 1995a). Furthermore, in a longitudinal study of 506 DS individuals, Coppus et al. (2006) reported a significant association between a history of depression and dementia. Those subjects with both dementia and depression were closely followed up to ensure that depression was not misdiagnosed as dementia, yielding an overall prevalence of depression of 22.7%.

Interestingly, a fourteen year longitudinal dementia follow-up in 77 female DS participants was recently published: depression was not significantly more prevalent in clinically demented subjects compared those without dementia. Indeed, in the most recent clinical assessment, including a psychiatrist report on depression, 49.3% of the demented subjects and 50% of the non-demented presented depression, although only eight subjects were still non-demented after fourteen years (McCarron, McCallion, Reilly, & Mulryan, 2014).

Irrespective of dementia, however, a particular vulnerability for depression has been suggested in adult DS individuals, which might obfuscate the relationship between depression and AD. Myers & Puschel (1991) reported a prevalence of 6.1% in 164 non-demented DS subjects over 20 years of age, but observed no depression in 261 DS individuals below 20 years of age. Others reported a three times higher number of depressed DS individuals (11.3%) compared to aged-matched controls with intellectual disability not due to DS (4.3%, Collacott et al., 1992). Later, Prasher & Hall (1996) found 5% as point prevalence of depression in DS. Nonetheless, Mantry et al. (2008) did not confirm this and demonstrated that depression in DS was even less common than in other intellectual disabilities, although statistical analysis were not performed due to a rather low number of subjects.

The prevalence of depression in adult DS individuals thus ranges between 5% and 50%, depending on diagnostic criteria, screening methodology (clinical observations, informant interviews etc.) and the particular study cohort. With a global point prevalence of major depressive disorder of 4.7% in the general population (Ferrari et al., 2013), depression is likely more common in DS. This higher prevalence might correspond to the increased co-morbid depression in MCI (16%) and AD (25%) in the general population (Van der Mussele et al., 2013a). Indeed, depression and dementia share various common symptoms, and depression can negatively, though reversibly, influence cognition and daily functioning. Therefore, depression might be misdiagnosed as dementia, pointing at the importance of careful differential diagnoses (Burt et al., 1992; Meins, 1995; Prasher, 2009). Whether the increased prevalence in DS relates to the early presence of neuropathological hallmarks of AD remains to be elucidated. Although the presence of depression, as such, may not be a predictive item for AD, (early) identification of depressive symptoms in DS is of utmost importance to enable therapeutic interventions, which may contribute to improvement of the quality of life.

### 5.3. Agitation and aggressiveness

Agitation and aggression occur in up to 60% of the AD patients in the general population, and this prevalence is affected by the residential situation, with a higher frequency in nursing homes (C. Ballard & Corbett, 2013; Cheng et al., 2009; Eustace et al., 2002; Mega et al., 1996). Among the demented DS population, a relatively high prevalence of agitated symptoms such as irritability and uncooperativeness has been suggested (Cooper & Prasher, 1998; Dalton & Crapper-McLachlan, 1986; Lai & Williams, 1989; Moss & Patel, 1995; Temple & Konstantareas, 2005). Indeed, Urv and co-workers (2010) reported agitation in 43.3% of the DS subjects with definite dementia, compared to 16.7% in those without.

In addition, increased aggression has been found in demented DS individuals (Dekker et al., 2015; Duggan et al., 1996; Urv et al., 2008, 2010). However, Cosgrave et al. (1999) showed that the presence of dementia is not predictive of aggression in DS. Indeed, others found no increased prevalence of aggression in demented DS subjects in comparison with non-demented DS individuals (Prasher & Filer, 1995) or with AD patients in the general population (Temple & Konstantareas, 2005). Cooper and Prasher (1998) even reported less aggression in a demented DS group than in demented individuals with intellectual disability of another aetiology.

The latter corresponds to the reduced prevalence of aggression found in the DS population, when dementia is not considered. Two large population-based studies showed that aggression was more than three times less likely to be present in DS subjects compared to individuals with intellectual disabilities related to other aetiologies (Collacott et al., 1998; Tyrer et al., 2006). Similarly, aggressive behaviour was independently associated with not having DS (Cooper et al., 2009). None of these three large scale studies reported the presence of clinical dementia symptoms, even though one attempted to take this into account by arbitrarily subdividing the cohort into two age groups (<35 and ≥35 years) and demonstrating a rather similar low prevalence of aggression in both groups.

Taken together, aggression is likely less present in the (non-demented) DS population. Agitation appears to be more prevalent in demented than in non-demented persons with DS. However, cross-sectional assessment of aggressive behaviour in demented DS cohorts yielded inconsistent results. This points at the necessity for longitudinal follow-up of DS individuals to establish a temporal relationship between agitation/aggression (frequency, severity) and the onset and progression of clinical dementia.

#### *5.4. Anxieties/phobias*

Up to half of the general AD population displays anxiety and phobias (Cheng et al., 2009; Eustace et al., 2002; Mega et al., 1996). Due to the fact that anxiety and phobias have hardly been investigated in DS, much remains unknown. In the few DS studies that did include this BPSD, no consistent prevalence data were reported. The only study comprehensively looking at anxiety and phobias in relation to AD demonstrated no significant difference in prevalence between AD patients with and without DS (Table 2; Temple & Konstantareas, 2005).

In the non-demented DS population, anxiety and phobias are less common. It is generally thought that with increasing age, externalizing behaviour decreases and internalizing behaviour, including anxiety, increases in DS (Visootsak & Sherman, 2007). However, in a DS group younger than 20 years, phobias were present in 1.5% of the cases, whilst in the group aged 20 years and older this decreased to 0.6% (Myers & Pueschel, 1991). A similarly low prevalence (1.5–2.7%) was reported by Mantry et al. (2008). Others longitudinally followed 52 DS subjects from childhood to adulthood (mean adult age: 26.6 years) and found that 10% showed phobic anxiety (McCarthy & Boyd, 2001). Adolescents and young adults with DS were also investigated by Capone and co-workers who reported significantly higher anxiety scores in DS subjects with major depression than in those without behavioural concerns (Capone et al., 2006). Finally, the use of a joint subscale for anxiety and depression revealed a significantly lower prevalence of anxious/depressive problems in late adolescents with DS compared to those without DS (van Gameren-Oosterom et al., 2013).

#### *5.5. Diurnal rhythm disturbances and sleep disorders*

In up to 40% of the AD patients in the general population, marked sleep disturbances have been reported (Moran et al., 2005; Shin et al., 2014). Similarly, an increased prevalence of sleep problems was found in the demented DS population (Cooper & Prasher, 1998; Deb et al., 2007; Dekker et al., 2015; Moss & Patel, 1995; Prasher & Filer, 1995; Temple & Konstantareas, 2005).

Among the non-demented DS population, a number of studies have demonstrated a high prevalence of sleep disturbances in children and adolescents with DS, including obstructive sleep apnoea (OSA), sleepdisordered breathing, bedtime resistance, sleep anxiety, daytime sleepiness, parasomnias and night waking (Breslin, Edgin, Bootzin, Goodwin, & Nadel, 2011; Carter, McCaughey, Annaz, & Hill, 2009; Chen, Spanò, & Edgin, 2013; de Miguel-Díez, Villa-Asensi, & Alvarez-Sala, 2003; Marcus, Keens, Bautista, von Pechmann, & Ward, 1991; McDowell & Craven, 2011). Reports on the altered sleep in DS adults, however, are scarce. In a rather small, not-population-based cohort of adult DS individuals, Trois et al. (2009) found an increased prevalence and severity of OSA in DS adults than in non-DS controls. Obstructive sleep apnoea syndrome, including sleep fragmentation, OSA, hypoventilation and hypoxemia was frequently observed. Strikingly, abnormal polysomnograms were observed in 94% of the DS adults. These sleep disturbances likely relate to the (developmental) anatomical abnormalities, general hypotonia and increased risk for obesity in DS (Trois et al., 2009).

Although these sleep disorders are not directly caused by dementia, they are very important to consider as they may aggravate cognitive decline. For instance, OSA in the general population is associated with increased cognitive impairment (Lal, Strange, & Bachman, 2012; Yaffe et al., 2011), and has been suggested to lead to prefrontal cortical dysfunction and subsequent executive dysfunction (Beebe & Gozal, 2002). Only recently, it has been argued that the relationship between poor sleep and cognitive decline is very worthwhile to investigate in DS (Fernandez & Edgin, 2013), but so far only a few efforts have been undertaken. Chen and co-workers (2013) found that increased OSA related to greater executive dysfunction (verbal fluency, inhibition) in older adolescents and younger adults with DS. Executive functioning is strongly associated with the prefrontal cortex and, as such, OSA may negatively affect this area. Consequently, the authors hypothesized that this early sleep disruption might advance dementia symptoms or enhance decline (Chen et al., 2013). Indeed, this would be in concordance with the previously discussed frontal lobe-associated BPSD, which were found as relatively early signs of AD in DS. Furthermore, obstructive sleep apnoea syndrome was significantly more present in adolescents and younger adults with DS and a diagnosis of major depressive episode, compared to those without depressive symptoms, suggesting that OSA might be a common comorbidity of depression in DS (Capone, Aidikoff, Taylor, & Rykiel, 2013).

In summary, sleep disturbances are omnipresent in the demented and non-demented DS population. Irrespective of its cause, sleep disorders have been described to significantly correlate with cognitive functioning and BPSD, such as apathy/indifference, depression and aggressiveness in the general population (Shin et al., 2014). As such, poor sleep probably aggravates cognitive decline and BPSD in DS as well. Due to the fact that non-demented DS subjects have a high risk to display sleep problems, the presence of sleep disorders does not likely differentiate between those with and without dementia. Therefore, longitudinal sleep studies are highly required to establish the change of sleep patterns, e.g. increased frequency or severity of OSA, in relation to the onset and progress of dementia in DS.

### *5.6. Psychosis, hallucinations, paranoia and delusions*

Psychotic symptoms, such as hallucinations and paranoid/delusional ideation have been reported in up to 45% of the non-DS AD patients – delusions being generally more common than hallucinations (Eustace et al., 2002; Gauthier et al., 2010; Mega et al., 1996; Van der Mussele, Mariën, et al., 2014b). Using the BEHAVEAD, Temple & Konstantareas (2005) studied BPSD in AD patients with DS (DS-AD) and without (AD-only). Delusions (AD-only: 80%, DS-AD: 43%) and hallucinations (AD-only: 53%, DS-AD: 23%) were relatively common and significantly lower in the DS-AD subjects (Table 2). Clustering the scores of delusions and hallucinations into one category of psychotic behaviour, and correcting for the severity of dementia, revealed that DS-AD individuals presented significantly less psychotic behaviour. Two other studies reported that delusions were present in resp. 37.5% and 58.3% and hallucinations in resp. 50% and 20.8% of the demented DS subjects (Duggan et al., 1996; Urv et al., 2010), which is significantly higher than in non-demented DS individuals. However, among those without dementia, delusions and hallucinations are not negligible. Urv et al. (2010) described that delusions and hallucinations were displayed in resp. 19.6% and 4.7% of the nondemented DS individuals. Moreover, it has been reported that not-otherwise-specified psychosis, including psychosis without depressive components, was present in 42% of a cohort of DS adolescents and young adults and the psychotic individuals were more apt to present visual and auditory hallucinations (Dykens, 2007). Conversely, three other studies reported no, or hardly any, psychotic behaviour in their adult DS cohorts (Haveman et al., 1994; Mantry et al., 2008; McCarthy & Boyd, 2001). Besides these studies and incidental case reports, psychotic behaviour has not been extensively studied yet. Even though psychotic behaviour is likely associated with dementia in DS, much remains unclear. Therefore, further research is required to establish its prevalence in non-demented DS individuals and how this may change over time in relation to the onset of dementia.

### *5.7. Appetite and eating abnormalities*

Altered eating behaviour is commonly observed in AD, including altered food intake, changing preferences and consumption of substances that are normally not eaten (pica) (Morris, Hope, & Fairburn, 1989). Although such behaviour causes great pressure on caregivers, changes in eating behaviour in the context of AD in DS have not received much attention so far. To our knowledge, only Duggan et al. (1996) published a more detailed report, including individual eating alterations amongst eight demented DS subjects. Most notably were three cases that left food unswallowed in their mouths, which was observed later in the course of dementia, and two subjects displaying pica – eating paper, table cloths or tampons for example. Only one DS individual did not show any changes in weight or eating behaviour, thus suggesting that eating behaviour is affected by dementia in DS (Duggan et al., 1996). Indeed, in a non-demented cohort of 186 DS individuals, no eating disorders or pica were observed (Mantry et al., 2008).

### *5.8. Disinhibition*

Disinhibition is a frontal lobe symptom that was found to be present in up to 45% of the AD patients in the general population and is generally more prevalent in FTD (Cummings, 1997; De Deyn et al., 2005a; Mega et al., 1996; Van der Mussele et al., 2013b). In DS, disinhibition is not comprehensively assessed and different studies reported on different features related to disinhibition – from impulsivity and reduced empathy to unacceptable habits – making comparisons rather hard. For instance, Urv et al. (2008) found more impulsivity in DS individuals with questionable dementia compared to their non-demented counterparts, suggesting that it might be an early symptom of AD in DS. Similarly, disinhibition features, including distractibility, disinhibition and impulsivity were markedly noted in non-demented DS subjects that presented one or more changes in behaviour and personality (Ball et al., 2008; Ball, Holland, Hon, et al., 2006). Remarkably, 95.7% of those with at least one behavioural change displayed disinhibited behaviour (Ball et al., 2010). In non-demented DS cohorts, however, disinhibition has hardly been studied. Compared to adolescents without DS, those with DS showed more attention problems, which included impulsiveness (van Gameraen-Oosterom et al., 2013). In addition, Fenner et al. (1987) reported strange and unacceptable (oral) habits, eccentric tendencies and improper body exposure, although this was likely related to the hospitalized setting.

### *5.9. Euphoria*

Euphoria, like disinhibition is less common in AD than in FTD. As such, the NPI and Middelheim Frontality Scale use euphoria as an item to differentiate between AD and FTD (Cummings, 1997; De Deyn et al., 2005a). De Deyn et al. (2005a) previously reported a prevalence of euphoria in AD patients of 44%, compared to 85.5% of the FTD patients. To the best of our knowledge, no reports on euphoria in DS have been published so far.

## **6. Clinical implications and future perspectives**

BPSD are associated with increased suffering, accelerated cognitive decline, earlier institutionalization and an increased mortality risk for patients, increased caregiver burden and higher costs (Finkel, 2000). In that context, accurate and early recognition of BPSD in DS may increase awareness and expand our understanding of the behavioural aberrations, thus enabling adaptive caregiving and, importantly, allowing for therapeutic interventions.

However, assessment of BPSD in DS is currently undervalued and far from accurate. This primarily relates to the evident lack of an all-embracing BPSD scale for DS. Other major issues concern (1) the frequent absence of baseline measures of pre-existing behaviour, making it harder to establish the extent of

deterioration, (2) the variable degree of intellectual disability, i.e. those with severe deficits may not understand verbal instructions and cannot (fully) express their feelings, (3) life events that especially affect (behaviour of) people with DS, (4) the questionable inter-informant reliability of various scales considering the high probability of caregiver changes and (5) a risk of minimization/downplaying of the significance of emotional disorders, and overreporting or exaggeration of BPSD (Auer et al., 1996; Aylward, Burt, Thorpe, Lai, & Dalton, 1997; Ekstein et al., 2011; Oliver et al., 2011; Prasher, 2009; Reisberg et al., 1996).

Based on this review, vast experiences in daily clinical practice, and the increased caregiver burden related to BPSD, the authors argue that accurate recognition and better evaluation of BPSD in DS are highly warranted. Unfortunately, behavioural evaluation scales for AD in the general population do not take the DS-specific circumstances into account, and existing scales for dementia in intellectual disabilities, such as the commonly used DMR (Evenhuis et al., 1998; Evenhuis, 1996), Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities (CAMDEX-DS; Ball, Holland, Huppert, Treppner, & Dodd, 2006; Ball et al., 2004) or Dementia Scale for Down Syndrome (DSDS; Gedy, 1995), are mainly functional and cognitive tools addressing behavioural alterations to a very limited extent. Consequently, the authors stress the considerable importance of developing a novel scale for BPSD in DS that specifically considers the challenges related to the pre-existing intellectual disability. Since activities of daily living, memory, orientation, language and perception are well-covered in the existing cognitive/functional DS questionnaires, a scale that exclusively focuses on behaviour would be most suitable. As such, it would serve as complementary module to any scale in use, and could thus be easily implemented in assessment procedures in routine practice. As described before, individuals with intellectual disabilities have difficulty expressing their emotions, causing the assessment of their behaviour to primarily rely on information from relatives and caregivers (Moss et al., 1993). Evaluating the pros and cons of patient interviews and informant interviews (see also section 3) and drawing on clinical experiences, the authors suggest that a structured, informant interview-based tool is the most preferred approach to systematically assess behaviour. Most importantly, such a scale should employ an all-embracing approach: not excluding any BPSD item in advance, and focussing on the identification of changes over time, i.e. disentangling behavioural alterations from characteristic behaviour that has always been typical for an individual. Accordingly, such an evaluation scale for BPSD in DS would serve a threefold purpose: (1) as clinical assessment tool to monitor behavioural changes in daily care, (2) as research tool in longitudinal follow-up studies, and (3) as comprehensive assessment tool for behavioural outcome measures in clinical trials for dementia in DS.

Firstly, extensive BPSD evaluation during regular follow-up visits, for instance in outpatient clinics, permits the identification of increases or decreases in frequency and/or severity of particular behaviour. Since BPSD are a major reason for referral (Adams et al., 2008), and caregivers often struggle to understand the change (Iacono, Bigby, Carling-Jenkins, & Torr, 2014), this would contribute hugely to improved awareness and understanding among relatives and caregivers. Iacono et al. (2014) found that professional caregivers generally have a limited understanding of the presentation of AD-related changes in DS, e.g. they often have difficulty understanding a resident's behaviour, and frequently wonder whether (challenging) behaviour is deliberate or attributable to dementia.

Apart from contributing to increased acceptance, meticulous BPSD evaluation would enable timely adaptation and optimization of daily caregiving, such as moving someone to a more suitable day-care centre or living accommodation, allocating increased time, and differently organizing the daily supervision and care in order to improve someone's personal environment (environmental management; Gauthier et al., 2010). Moreover, it would also allow for specific therapeutic interventions. While cognitive deterioration in AD cannot yet be prevented, various behavioural, educational and pharmacological options are available to reverse or reduce particular BPSD (Gauthier et al., 2010; Nowrangi, Lyketsos, & Rosenberg, 2015).

Consequently, this would reduce the BPSD-related distress and may improve quality of life. But how to select the most appropriate intervention? Iacono et al. (2014) interviewed professional caregivers and reported that their management strategies were often based on trial and error. Since publications on BPSD management in DS are scarce, studies on management of BPSD in the general AD population (extensively reviewed in: Gauthier et al., 2010; Nowrangi et al., 2015) may provide some directions. Gauthier et al. (2010) stressed the lack of consensus regarding treatment approaches. Non-pharmacological interventions, such as behavioural therapy, psychosocial interventions or music therapy, are generally applied first, followed by, or in conjunction with, medication (Gauthier et al., 2010). Although particular BPSD can be targeted using specific pharmacological agents, e.g. antidepressants, antipsychotics or anxiolytics, the risk/benefit trade-offs have to be carefully assessed. For instance, a recent study with 98 intellectually disabled individuals found that discontinuation of antipsychotic treatment for challenging behaviour related to improved behavioural functioning (de Kuyper, Evenhuis, Minderaa, & Hoekstra, 2014).

Secondly, future longitudinal studies using a specific evaluation scale for BPSD in DS would allow for the establishment of the temporal relationship between the presence of particular BPSD and the moment of the clinical diagnosis of AD dementia in DS. Accordingly, this enables the identification of particular BPSD as early behavioural indicators for clinical AD (Jost & Grossberg, 1996), possibly corroborating the aforementioned findings of frontal lobe symptoms as early changes of AD in DS. Such longitudinal approaches are highly necessary, since only sustained follow-up studies (multiple years) may identify predictive symptoms,

as demonstrated by our group in a ten-year follow-up study of an AD cohort in the general population (Engelborghs et al., 2005; Van der Mussele, Franssen, et al., 2014; Van der Mussele, Mariën, et al., 2014a). Finally, an all-embracing scale for BPSD in DS could greatly improve the monitoring of behavioural outcome measures in clinical trials. In the general AD population, the BEHAVE-AD and NPI are frequently used in large-scale clinical trials for new psychotropic medication (Cumbo & Lorigi, 2014; De Deyn & Wirshing, 2001; Porsteinsson et al., 2014; Sultzer et al., 2008). For instance, risperidone, an atypical antipsychotic drug, has been previously demonstrated to significantly reduce agitation, aggression and psychosis-associated symptoms in AD patients in the general population, as well as reduce overall BEHAVE-AD scores, which is indicative of an improving BPSD profile (De Deyn et al., 1999, 2005b; Rabinowitz et al., 2007). In agreement, others reported that risperidone treatment of AD patients resulted in reduced NPI total scores, which, again, indicates beneficial symptomatic effects on the overall presence of BPSD (Sultzer et al., 2008). Currently, two phase II clinical trials on cognitive enhancement in DS are ongoing: one using the green tea flavonol epigallocatechin-3-gallate (EGCG) (De la Torre et al., 2014; Parc de Salut Mar, 2012: NCT01699711) and the CLEMATIS study using the GABA<sub>A</sub>  $\alpha$ 5 receptor inverse agonist RG1662 (Ballard et al., 2009; Hoffmann-La Roche, 2013: NCT02024789). Importantly, behaviour is included in the primary outcome measures in both trials. More specifically, the EGCG trial uses 'change in cognitive evaluation', which includes a neuropsychiatric evaluation based on, amongst others, DMR and NPI scores. The RG1662 study evaluates adaptive behaviour. Whereas both trials focus on cognitive enhancement with respect to the congenital intellectual disability, the EGCG trial also evaluates the effect of EGCG on the deceleration of AD progression in DS. Despite the fact that the DMR (not inclusive) and NPI (not adapted) sub-optimally assess BPSD in DS, these scales remain to be employed given the lack of more optimal measures. Therefore, a novel, comprehensive scale to assess BPSD in DS would be very valuable.

## **7. Neurobiology of BPSD in DS**

Unravelling the underlying neurobiological mechanisms of BPSD in DS would contribute to the general understanding of these burdensome behavioural and psychological changes and aid the development of targeted therapeutic, and possibly preventive, interventions. An increasing number of studies addressed the mechanisms of BPSD in AD, for instance pointing at specific dysregulated monoaminergic neurotransmitter systems (Vermeiren et al., 2014a, 2014b). In agreement, we recently reported multiple correlations between monoaminergic changes in serum of demented, converted and non-demented DS subjects and individual BPSD items (Dekker et al., 2015). Furthermore, GABAergic neurotransmission appears to be altered in DS brain and has been implicated in learning and memory deficits (reviewed in: Martínez-Cué et al., 2014). GABA is the major inhibitor neurotransmitter in the adult forebrain, and as such, its altered neurotransmission will likely affect behaviour as well.

In addition, frontal lobe dysfunction has been suggested as early manifestation of AD in DS (Ball et al., 2008; Ball, Holland, Hon, et al., 2006; Deb et al., 2007; Nelson et al., 2001). Indeed, it is thought that lesions in the complex frontal-subcortical neuronal circuits cause particular behavioural alterations, i.e. impairment of the anterior cingulate circuit is associated with apathy, lesions in the lateral orbitofrontal circuit cause disinhibition and reduced empathy, and disruption of the dorsolateral prefrontal circuit relates to executive dysfunction (Tekin & Cummings, 2002). This led Ball and co-workers to suggest that 'the serotonergically mediated orbitofrontal circuit may be disproportionately affected' in DS as disinhibited behaviour was markedly present, relative to the apathy and executive dysfunction, in non-demented DS subjects with one or more behavioural change(s) (Ball et al., 2010), thus again pointing in the direction of altered neurotransmission. Alternatively, the symptoms related to frontal lobe dysfunction in DS might be explained by preexisting abnormalities in the DS brain, which may modulate the effect of AD dementia on behavioural changes associated with prefrontal cortex functioning. Indeed, people with DS have a reduced volume of the frontal cortex (Beacher et al., 2010) and therefore only a small additional neuropathology, such as accumulation of A $\beta$ , may have a makeable impact in its functionality (Lott & Head, 2001). For this reason functional impairments of frontal cortical regions may coexist with the development of AD in DS.

Although mechanisms similar to those in AD patients may underlie BPSD in DS, the supplementary effect of the overexpressed chromosome 21 gene products has not yet been investigated. In addition to their altered genetics, mounting evidence suggests the presence of epigenetic aberrations in DS, which appear to be important factors in the development of the cognitive deficits in DS (Dekker, De Deyn, & Rots, 2014) and might also affect DS behaviour. Future studies that specifically address DS, taking their unique genetic background into account, are necessary to further elucidate the neurobiology of BPSD in DS.

## **8. Conclusion**

In conclusion, BPSD are a core symptom of dementia in addition to cognitive decline and impaired activities of daily living, and are extensively studied in MCI and AD patients in the general population. Despite the extremely high risk to develop AD and the lack of early (bio)markers with limited invasiveness to predict the onset of AD in DS, most dementia research in the DS population did not comprehensively assess BPSD. The great variety of cohorts, diagnostic methodologies, covariates and outcome measures that have been used in the available BPSD studies in DS yielded diverse results and made comparisons generally hard to accomplish. Due to the multitude of applied, sub-optimal scales, it is questionable whether BPSD have always been accurately assessed, for instance regarding the differential diagnosis between apathy and depression. Interstudy

comparisons are additionally complicated by the fact that control groups varied between these studies, from non-demented DS individuals and intellectually disabled persons with other aetiologies, to AD patients in the general population.

Various BPSD appear to be altered in demented DS individuals, but study results have not always been consistent. Based on the existing literature, Figure 1 summarized the temporal relationship between BPSD and the clinical diagnosis of AD. From childhood to adulthood, externalizing behaviour likely decreases and internalizing behaviour increases. Frontal lobe symptoms have been suggested as early signs of AD in DS. Indeed, disinhibition and apathy, as well as executive dysfunction, seem to be omnipresent in the prodromal phase, whereas reports are still too divergent to assume that this is also true for depression. Regarding activity disturbances, various studies indicated decreasing hyperactivity levels towards adulthood in DS. Excessive activity in demented DS individuals would thus be a fairly easy observable sign. However, general slowness in this group has been reported as well. In addition, the presence of apathy itself might cause reduced activity. Agitation appears to be more prevalent in demented than in non-demented DS individuals, but reports on aggression are inconsistent, though aggression seems to be reduced in the overall DS population. Sleep disturbances are markedly present in both demented and non-demented DS individuals. Although sleep disorders may not yet differentiate between those with and without AD, they are important to consider as such sleep disorders may aggravate cognitive decline and BPSD. Next, a higher prevalence of psychotic symptoms (delusions and hallucinations) is likely observed in DS persons with dementia than among those without dementia. Finally, anxiety and phobias, appetite and eating abnormalities and euphoria have been hardly studied in DS and DS-AD.

Taken together, the need for a validated and comprehensive scale for BPSD in DS is evident. The limited current understanding and the vast amount of (inconsistent) reports discussed in this review illustrate the vital importance for an all-inclusive scale that does not omit specific BPSD items in advance, and that focuses on individual changes over time, disentangling those changes from someone's typical behaviour. Once BPSD can be meticulously assessed in DS, longitudinal studies are of utmost importance to establish the temporal relationship between BPSD and the clinical dementia diagnosis, likely revealing early signs of AD in DS. Such signs are of great value, as they may serve as early clinical indicators for AD in DS, thereby enabling adaptive caregiving and early therapeutic interventions.

#### **CAPTION FIGURE 1**

**Fig.1: Temporal relationship between BPSD and the clinical diagnosis of AD in DS.** From childhood towards adolescence and early adulthood, externalizing behaviour decreases and internalizing behaviour increases. In non-demented adults with DS, apathy, disinhibition and executive dysfunction have been reported as early behavioural symptoms, possibly predictive for the onset of dementia. Agitation, hyperactivity/general slowness and psychotic symptoms seem to be more prevalent in demented DS individuals. Sleep disturbances have been described throughout life. Anxiety and phobias, appetite and eating abnormalities and euphoria have been hardly studied in DS and DS-AD.

#### **Conflict of interest**

The authors herein declare no conflict of interest.

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Table 1: Overview of BPSD items in BEHAVE-AD and NPI scales

**Behavioural Pathology in Alzheimer's Disease Rating Scale**

**(BEHAVE-AD)**

**Neuropsychiatric Inventory (NPI)**

Activity disturbances

*Incl. purposeless activity, inappropriate activity, wandering*

Aberrant motor behaviour

Affective disturbances

*Incl. depression, tearfulness*

Apathy  
 Depression/dysphoria  
 Aggressiveness  
*Incl. agitation, physical aggression, verbal aggression*  
 Agitation/aggression  
 Irritability/lability  
 Anxieties/phobias Anxiety  
 Diurnal rhythm disturbances Night-time behaviour disturbances  
 Hallucinations  
*Incl. auditory, haptic, olfactory and visual hallucinations*  
 Hallucinations  
 Paranoid and delusional ideation  
*Incl. delusions of all kinds, like stealing and abandonment*  
 Delusions  
 Appetite/eating disturbances  
 Disinhibition  
 Euphoria/elation  
 (Cummings, 1997; Cummings et al., 1994; Kaufer et al., 2000; Reisberg et al., 1987; Reisberg, Auer, & Monteiro, 1996)

## Tables

Table 1: Overview of BPSD items in BEHAVE-AD and NPI scales

Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)	Neuropsychiatric Inventory (NPI)
Activity disturbances <i>Incl. purposeless activity, inappropriate activity, wandering</i>	Aberrant motor behaviour
Affective disturbances <i>Incl. depression, tearfulness</i>	Apathy Depression/dysphoria
Aggressiveness <i>Incl. agitation, physical aggression, verbal aggression</i>	Agitation/aggression Irritability/lability
Anxieties/phobias	Anxiety
Diurnal rhythm disturbances	Night-time behaviour disturbances
Hallucinations <i>Incl. auditory, haptic, olfactory and visual hallucinations</i>	Hallucinations
Paranoid and delusional ideation <i>Incl. delusions of all kinds, like stealing and abandonment</i>	Delusions
	Appetite/eating disturbances
	Disinhibition
	Euphoria/elation

(Cummings, 1997; Cummings et al., 1994; Kaufer et al., 2000; Reisberg et al., 1987; Reisberg, Auer, & Monteiro, 1996)

Table 2: Cross-sectional approaches assessing BPSD in relation to dementia in DS

Study reference	Study population(s)	BPSD assessment †	Main results
(Dalton & Crapper-McLachlan, 1986)	35 DS from published studies between 1946 and 1985: 13♂/35 - 33 neuropathological AD confirmation - 25 clinically demented	Summary of case reports with clinical information	Among the DS with neuropathological confirmation of AD and those with clinical dementia, personality changes were presented by resp. 45.5% and 56%, apathy/inactivity (36.4%, 48%), stubbornness/uncooperativeness (21.2%, 28%), walking impairment (18.2%, 24%), memory loss (18.2%, 24%), depression (18.2%, 20%), disorientation (12.1%, 16%) and hallucinations/delusions (3%, 4%).
(Lai & Williams, 1989)	96 DS: 61♂/96, > 35 yrs, 49 demented (27♂/49, dementia onset: 54.2 ± 6.1 yrs)	Neurological assessment, informant interviews	Early phases of AD, including (mild) memory decline, was likely masked due to poor language skills. Initial signs were primarily changes in personality, incl. emotional lability and irritability. In those with more severe ID, the first presentation of dementia concerned apathy, inattention and decreased social interactions.
(Haveeman et al., 1994)	1580 ID: group homes (106 DS, 733 non-DS), institutes (201 DS, 541 non-DS)	Gerontological Questionnaire	Compared to non-DS persons with ID, DS showed more apathy, drowsiness, fear, incoherent behaviour, irritation, lack of appetite, night-time restlessness, sadness, suspiciousness with advancing age.
(Prasher & Filer, 1995)	15 demented DS: 3♂/15, 54.2 ± 8.6 yrs 25 non-demented DS: 14♂/25, 51.4 ± 9.1 yrs	Nygaard scale	Compared to the non-demented group, demented DS showed increased day-time wandering, low mood, difficulty finding way around home, sleep disturbances and easy tiredness.
(Moss & Patel, 1995)	12 ID with dementia, 5/12 had DS 87 ID without dementia, 4/87 likely DS	PAS-ADD	Compared to controls, people with ID and dementia were more likely to suffer from loss of interest, irritability, slowness, and sleep difficulties, and less likely to present delayed sleep and depressed mood.
(Duggan, Lewis, & Morgan, 1996)	12 demented people with mild to moderate ID: 3♂/12, 59.9 (48-77) yrs, 8/12 had DS  Among the DS individuals: 1♂/8, 56.5 (48-65) yrs	PBHI	Symptoms in demented individuals (DS between brackets) with the mean duration (range between brackets) in months with respect to dementia onset: Aggression: 9/12 subjects (6 DS), mean: 20.6 (3-36). Delusions: 3/12 (3 DS), mean: 14 (12-18). Depressed mood: 3/12 (3 DS), mean: 15 (6-36). Diurnal rhythm disturbances: 6/12 (? DS), mean: 13.7 (2-30). Eating disturbances: 5/12 (3 DS) left food unswallowed in mouth, mean: 15.4 (1-36). Hallucinations: 4/12 (4 DS), mean: 13 (4-18). Misplacing objects: 6/12 (? DS), mean: 17.2 (8-36).
(Cooper & Prasher, 1998)	19 demented DS: 5♂/19, 57 ± 9.3 yrs 26 non-DS persons with ID and dementia: 9♂/26, 77.4 ± 8.8 yrs	PPS-LD, DAS, DMR and Nygaard scale	Compared to controls, demented DS subjects showed: ↑ low mood ↑ restlessness/excessive overactivity ↑ disturbed sleep ↓ aggression
(Holland et al., 1998)	75 DS: 43♂/75, ≥ 30 yrs - 18/75 (24.3%) demented	CAMDEX, CAMCOG neuropsychological test battery, VABS	49/75 (65.3%) presented changes in at least one out of four domains: personality/behaviour, memory, daily living skills and general mental functioning. 35/49 (71%) presented first changes in behaviour and personality (specified in ref.). Among the demented subjects (n=18), 13 subjects (72.2%) presented behaviour and personality changes.
(Cosgrave et al., 1999)	128 DS: 54♂/128, moderate ID (23 demented, 57.256.1 yrs; 49 non-demented, 48.426.9 yrs), severe ID (6 demented, 53.5 ± 4.7 yrs; 50 non-demented, 46.8.3 yrs)	BARS and ABS Part 2	No increase in behavioural disturbances in demented, compared to non-demented individuals. Agitation/aggression did not discriminate between the presence or absence of dementia.
(Huxley et al., 2005)	34 DS - 15 demented, 8♂/15, 52.8 ± 10.32 yrs - 19 non-demented, 12♂/19, 46.0 ± 8.72 yrs	ABC-Community Version	Compared to non-demented DS, demented DS presented a significantly higher severity and frequency for lethargy (P=0.001; P=0.001), hyperactivity (P=0.004; P=0.003), the difference for stereotypy (P=0.051; P=0.060) and irritability (P=0.080; P=0.065) was almost significant.
(Temple & Konstantareas, 2005)	30 AD with DS (DS-AD): more females, not specified, 52 yrs  30 AD without DS (AD-only): more females, not specified, 80 (57-93) yrs	Clinical observations at day-care programs, BEHAVE-AD and apathy subscale of the CERAD Behavioural Rating Scale for Dementia	BEHAVE-AD/CERAD scores: activity disturbances (AD-only: 60%, DS-AD: 87%, P=0.02), aggressiveness (AD-only: 66%, DS-AD: 66%, n.s.), anxiety and phobias (AD-only: 83%, DS-AD: 66%, n.s.), delusions (AD-only: 80%, DS-AD: 43%, P=0.003), diurnal rhythm disturbances (AD-only: 53%, DS-AD: 66%, n.s.), hallucinations (AD-only: 53%, DS-AD: 23%, P=0.02) and apathy (AD-only: 90%; DS-AD: 87%, n.s.). Affective disturbances from the BEHAVE-AD were not reported due to low reliability. BEHAVE-AD/CERAD scores combined into three categories and compared between the groups: (1) Aberrant behaviour: activity disturbances, diurnal rhythm disturbances, apathy (P=0.51); (2) Psychotic behaviour: delusions, hallucinations (P<0.001 – significantly less in DS-AD); (3) Reactive behaviour: aggression, anxiety/phobias (P=0.20). Day program observations: DS-AD showed significantly increased purposeful (P=0.009) and non-purposeful motor behaviour (P=0.04); decreased high mood (P=0.03) and observations of others (P=0.001).
(Jozsvai, 2006)	19 demented DS: 10♂/19, 53.9 ± 5.7 yrs 45 demented without ID: 21♂/45, 76.7 ± 9.9 yrs	BEAM-D	Compared to demented persons without ID, demented DS displayed significantly more frequent and severe non-compliant behaviour (P<0.03; P<0.01), more severe property destruction (P<0.01) and less severe insomnia (P<0.00).
(Deb et al., 2007)	Interview with 24 main caregivers of 24 demented DS subjects (<50 yrs: 1; 50-60 yrs: 18; >60 yrs: 5)	Qualitative interviews with major caregivers	In the early stage of the disease, memory problems were most evident: loss of recent memory with relative intactness of distant memory. Caregivers particularly reported increased confusion, covering up for memory loss

		about behavioural changes in the demented subjects	(excusing, confabulation), emotional problems, forgetfulness, hallucinations (tactile, visual) and illusions, lack of confidence, loss of interest/motivation, obsessive symptoms, personality changes (loss of mischievousness), sleep problems, general slowness of daily functioning (eating, motor functioning, speaking etc.) and socializing problems/withdrawal.																																																																						
(Urv et al., 2008)	251 DS - 161 no dementia, ♂: 21.7%, 51.6 ± 5.7 yrs. - 52 questionable dementia, ♂: 28.8%, 54.7 ± 7.8 yrs - 14 possible dementia, ♂: 42.9%, 61.1 ± 7.3 yrs - 24 definite dementia, ♂: 29.2%, 59.1 ± 8.12 yrs	ABS, DMR, Stress Index, RSMB	Major maladaptive behaviour: lowest in demented group, increased in number with dementia status and highest in those with definite dementia. To track early signs of AD, the non-demented and questionable groups were compared: higher number of regressive behaviour, inattentiveness, low energy, non-assertiveness, withdrawal, destructiveness, hostility, impulsivity, object attachment, aggressive behaviour and body stress in those with questionable dementia. Larger number of physical depression symptoms in questionable, possible and definite dementia groups																																																																						
(Urv et al., 2010)	224 DS - 125 no dementia, ♂: 15.9%, 54.0 ± 5.0 yrs. - 44 questionable dementia, ♂: 25%, 56.7 ± 6.7 yrs. - 25 possible dementia, ♂: 28%, 57.9 ± 5.4 yrs. - 30 definite dementia, ♂: 20%, 60.0 ± 6.8 yrs.	CUSPAD	No differences in behavioural disturbances, delusions, depression, hallucinations and illusions with regard to sex or the level of intellectual functioning.																																																																						
			<table border="1"> <thead> <tr> <th></th> <th>Dementia:</th> <th>No</th> <th>Questionable</th> <th>Possible</th> <th>Definite</th> <th>P-value</th> </tr> </thead> <tbody> <tr> <td>Behavioural disturbance</td> <td>28%</td> <td>47.7%</td> <td>60%</td> <td>60%</td> <td>60%</td> <td>&lt;0.001</td> </tr> <tr> <td>- Agitation</td> <td>16.7%</td> <td>31.8%</td> <td>8%</td> <td>43.3%</td> <td>43.3%</td> <td>&lt;0.001</td> </tr> <tr> <td>- Night confusion</td> <td>3.2%</td> <td>2.3%</td> <td>20%</td> <td>23.3%</td> <td>23.3%</td> <td>&lt;0.001</td> </tr> <tr> <td>- Violence</td> <td>7.9%</td> <td>20.5%</td> <td>24%</td> <td>16.7%</td> <td>16.7%</td> <td>&lt;0.05</td> </tr> <tr> <td>- Wandering</td> <td>0.8%</td> <td>2.3%</td> <td>8%</td> <td>16.7%</td> <td>16.7%</td> <td>&lt;0.001</td> </tr> <tr> <td>Delusions</td> <td>19.6%</td> <td>31.4%</td> <td>45.5%</td> <td>58.3%</td> <td>58.3%</td> <td>&lt;0.001</td> </tr> <tr> <td>Depression</td> <td>18.4%</td> <td>25%</td> <td>44%</td> <td>60%</td> <td>60%</td> <td>&lt;0.001</td> </tr> <tr> <td>- Non-event related sadness</td> <td>18.8%</td> <td>75%</td> <td>83.3%</td> <td>100%</td> <td>100%</td> <td>&lt;0.001</td> </tr> <tr> <td>Hallucinations</td> <td>4.7%</td> <td>14.3%</td> <td>13.6%</td> <td>20.8%</td> <td>20.8%</td> <td>&lt;0.05</td> </tr> </tbody> </table>		Dementia:	No	Questionable	Possible	Definite	P-value	Behavioural disturbance	28%	47.7%	60%	60%	60%	<0.001	- Agitation	16.7%	31.8%	8%	43.3%	43.3%	<0.001	- Night confusion	3.2%	2.3%	20%	23.3%	23.3%	<0.001	- Violence	7.9%	20.5%	24%	16.7%	16.7%	<0.05	- Wandering	0.8%	2.3%	8%	16.7%	16.7%	<0.001	Delusions	19.6%	31.4%	45.5%	58.3%	58.3%	<0.001	Depression	18.4%	25%	44%	60%	60%	<0.001	- Non-event related sadness	18.8%	75%	83.3%	100%	100%	<0.001	Hallucinations	4.7%	14.3%	13.6%	20.8%	20.8%	<0.05
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Hallucinations	4.7%	14.3%	13.6%	20.8%	20.8%	<0.05																																																																			
(Oliver et al., 2011)	36 DS: 12 younger non-demented: 8♂/12, 34.9 ± 4 yrs; 12 older non-demented: 4♂/12, 51.6 ± 5.7 yrs; 12 demented: 5♂/12, 49 ± 7.4 yrs.	AADS, DMR, VABS	Based on AADS, a significantly higher number, frequency and management difficulty of behavioural excesses and deficits in the demented group than in both groups without dementia. Scores and statistical differences for individual BPSD items were not described.																																																																						
(Dekker et al., 2015)	Cross-sectional blood sampling and longitudinal clinical follow-up: 151 DS 51 demented at baseline: 30♂/51, 54.2 (49.7-58.4) yrs; 50 converted to AD: 27♂/50, 52.1 (48.4-55.8) yrs; 50 non-demented: 29♂/50, 49.4 (46.3-51.6) yrs.	DMR, SRZ, VABS	Compared to converted and non-demented DS, demented DS presented: ↑ diurnal rhythm disturbances (P=0.004) ↑ apathy (P=0.008) ↑ aggressiveness (P=0.008). Isolation was the least common in the converted DS group (P=0.0004).																																																																						

† Only the scales that (partially) assess one or more BPSD items (as listed in Table 1) are listed, thus omitting those that assess cognitive decline in dementia, executive functioning or daily living skills. AADS, Assessment for Adults with Developmental Disabilities; ABC, Aberrant Behaviour Checklist; ABS, Adaptive Behaviour Scale; BARS, Brief Agitation Rating Scale; BEAM-D, Behavioural and Emotional Activities Manifested in Dementia Scale; CAMCOG, Cambridge Cognitive Examination; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly; CUSPAD, Columbia University Scale for Psychopathology in Alzheimer's Disease; DAS, Disability Assessment Schedule; DMR, Dementia Questionnaire for Mentally Retarded People; ID, intellectually disability; PAS-ADD, Psychiatric Assessment Schedule for Adults with a Developmental Disability; PBHI, Past Behavioural History Inventory; PPS-LD, Present Psychiatric State for adults with Learning Disabilities; ref., reference; RSMB, Reiss Screen for Maladaptive Behaviour; SRZ, Social Competence rating scale; VABS, Vineland Adaptive Behaviour Scales.

Table 3: Longitudinal approaches assessing BPSD in relation to dementia in DS

Study reference	Study population(s)	BPSD assessment †	Main results												
(Evenhuis, 1990)	17 middle-aged DS, who died at ≥40 yrs: 7♂/17, 14/17 developed AD	Clinical evaluation, neurological examination and, if institutionalized, informant interviews (≥ 2 nurses, ≥ 2/year)	<table border="1"> <thead> <tr> <th></th> <th>1<sup>st</sup> year AD</th> <th>2<sup>nd</sup> year AD</th> <th>≥3<sup>rd</sup> year of AD</th> </tr> </thead> <tbody> <tr> <td>Moderate retardation (n=9)</td> <td>Apathy, withdrawal 8 Irritability, aggression 2 Daytime sleepiness 4</td> <td>0 2 3</td> <td>0 3 1</td> </tr> <tr> <td>Severe retardation (n=5)</td> <td>Apathy withdrawal 5 Irritability, aggression 1 Daytime sleepiness 3</td> <td>0 1 1</td> <td>0 0 0</td> </tr> </tbody> </table>		1 <sup>st</sup> year AD	2 <sup>nd</sup> year AD	≥3 <sup>rd</sup> year of AD	Moderate retardation (n=9)	Apathy, withdrawal 8 Irritability, aggression 2 Daytime sleepiness 4	0 2 3	0 3 1	Severe retardation (n=5)	Apathy withdrawal 5 Irritability, aggression 1 Daytime sleepiness 3	0 1 1	0 0 0
	1 <sup>st</sup> year AD	2 <sup>nd</sup> year AD	≥3 <sup>rd</sup> year of AD												
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Severe retardation (n=5)	Apathy withdrawal 5 Irritability, aggression 1 Daytime sleepiness 3	0 1 1	0 0 0												
(Visser et al., 1997)	307 DS: 175♂/307, 38.4 ± 11.4 yrs 56/307 developed dementia: 56.1 ± 7.4 yrs	Early Signs of Dementia Checklist	Among the demented DS, decreased interest was displayed by resp. 72% at the onset of deterioration and 100% at the onset of distinctive dementia, decreased general pace and motivation (resp. 62%, 90%), exaggeration of character traits (24%, 76%), mood changes (28%, 82%), increased excitability (15%, 53%), emotional instability (14%, 57%), reversal of day-night rhythm (6%, 26%) and nocturnal anxiety (7%, 36%).												
(Holland et al., 1998)	Baseline (t=0) 75 DS: 43♂/75, ≥ 30 yrs 18/75 (24.3%) demented	CAMDEX, CAMCOG, VABS	At baseline 49/75 (65.3%) presented changes in at least one out of four domains: personality/behaviour (specified in ref.), memory, daily living skills and general mental functioning. Among the demented population (n=18), 13 subjects (72.2%) presented personality/behaviour changes.												
(Holland et al., 2000)	Follow-up (t=18 months) 68 DS: 41♂/68, 42.3 ± 8.3 yrs 26/68 (38.2%) demented		Follow-up observations in age groups 30-39 (n=24) and 40-49 yrs (n=29), as compared to baseline: no decline (resp. 41.7%, 3.5%), only memory decline (4.2%, 3.5%), only personality changes (29.2%, 31%), only memory and personality change (0%, 10.4%), memory decline and changes in ≥2 areas (12.5%, 10.4%); changes in ≥2 areas, but no memory decline (12.5%, 6.9%)												
(Ball et al., 2006)	Follow-up (t=5 years) 55 DS: 34♂/55, 48.3 (36-72) yrs 10/55 (18%) demented, 4 of whom had AD at baseline		Among the 51 DS that were non-demented at baseline, 30/51 (58.8%) presented one or more changes in personality and behaviour (specified in ref.), of which 11/51 (21.6%) met FTD criteria, whereas 21/51 (41.2%) exhibited no changes at t=0. ≥1 symptom: 59%; ≥5 symptoms: 22%. With a FTD diagnosis at baseline, subjects have >1.5 increased risk to progress to AD over 5 years. With at least one behaviour/personality change at baseline, subjects have >1.5 risk to develop FTD, memory decline or AD over 5 years.												
(Ball et al., 2008)	Cross-sectional and partially longitudinal: 103 DS - 25 AD, 55 ± 5.6 yrs - 78 non-AD, 47 ± 7.6 yrs	CAMDEX-DS, neuropsychological assessments, FTD-checklist of Gregory & Hodges	Among the 78 non-demented DS, 28 (35.9%) had no changes in either memory or behaviour/personality, 3 (3.8%) had memory changes without altered behaviour/personality, and 47 (60.3%) had ≥ 1 change in behaviour/personality (specified in ref.), of which 14 (29.8%) also in memory. The number of behaviour/personality changes in the non-demented DS group significantly predicted the performance on two executive function tasks and two executive memory tests.												
(Nelson et al., 2001)	26 DS: 10♂/26, 40.3 ± 11.2 yrs Two groups established at t=1 (baseline): - 9 DS with abnormal physical findings (MRI atrophy and pathological reflexes) - 17 DS without physical abnormalities	NBAP at two time points (t=1 and t=2, one year apart).	No reported dementia diagnostics. However, cognitive functioning (incl. memory) was significantly lower in the group with abnormal physical findings, indicating probable dementia. Compared to the physically normal group, those with abnormal physical findings presented: ↑ indifference, e.g. apathy (t=1, P=0.038; t=2, P=0.002) ↑ depression, e.g. dysphoric mood and loss of pleasure (t=1, P=0.017; t=2, P=0.016)												
(Urv et al., 2008)	Follow-up (14-18 months): 161 non-demented DS - 101 non-converters; 37 converters from no dementia to questionable dementia	RSMB	Compared to the non-converters, the converters presented significantly more confused thinking, dependence, fearfulness, object attachment, regressive behaviour, sadness and social inadequacies.												
(Adams & Oliver, 2010)	30 non-demented DS: 15♂/30, 44.5 ± 7.5 yrs. Follow-ups at 8 and 16 months: cognitive deterioration between baseline and 16 months in n=10	AADS, NAID, VABS	The frequency of behavioural excesses and deficits (not specified) was significantly increased in 16 months, only in those with (early) cognitive deterioration; not in those without deterioration. A decrease in executive function measures was correlated with increased behavioural excesses in those with cognitive deterioration.												

† Only the scales that (partially) assess one or more BPSD items (as listed in Table 1) are listed, thus omitting those that assess cognitive decline in dementia, executive functioning or daily living skills. AADS, Assessment for Adults with Developmental Disabilities; CAMCOG, Cambridge Cognitive Examination; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly; CAMDEX-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; FTD, Frontotemporal dementia; NAID, Neuropsychological Assessment of Dementia in Individuals with Intellectual Disabilities; NBAP, Neuropsychology Behaviour and Affect Profile; ref., reference; RSMB, Reiss Screen for Maladaptive Behaviour; VABS, Vineland Adaptive Behaviour Scales.

Table 4<sup>†</sup>: Behavioural and psychiatric disorders in DS without dementia

Study reference and design	Study population(s)	Behavioural and psychological scale	Main results
(Fenner et al., 1987)	Cross-sectional: 39 hospitalized DS, 21♂/39, 36.7 (19.3-43.9) yrs, mean length hospital stay: 26.4 yrs	ABS Part 2	Activity disturbances: hyperactivity (8%), removes/tears off own clothing (15%), stereotyped behaviour (44%). Affective disturbances: withdrawal (18%), inactivity (39%), aggression: threatening/physical violence (28%), violent tempers or tantrums (28%), angry language (18%), damages personal property (13%), damages others' property (8%), damages public property (15%). Others: peculiar posture or odd mannerisms (13%), disturbing vocal or speech habits (36%), strange and unacceptable habits (49%), unacceptable oral habits (18%), other eccentric habits and tendencies (26%), exposes body improperly (15%). 17/39 (44%) presented minimally disturbed behaviour.
(Myers & Pueschel, 1991)	Cross-sectional: 497 DS - 261 (52.5%): < 20 years - 164 (35.1%): ≥ 20 years	DSM-III-R criteria	Aggressiveness (< 20 yrs, 6.5% vs. ≥ 20 yrs, 6.1%), attention deficit disorder (6.1% vs. 2.4%), conduct/oppositional disorder (5.4% vs. 1.8%), stereotypic behaviour (2.7% vs. 4.3%), phobias (1.5% vs. 0.6%) and major depressive disorder (0% vs. 6.1%).
(Collacott et al., 1992)	Cross-sectional: 371 DS, ♂53%, 36.3 ± 11.25 yrs; 371 ID of other aetiologies: ♂53%, 36.3 ± 11.18 yrs	Case records, retrospective assessment (ICD-9)	No disorder (DS, 74.1% vs. non-DS, 62.3%; P=0.001), depression (11.3% vs. 4.3%; P=0.001), conduct disorders (6.2% vs. 20.5%; P<0.001), presenile dementia (4.3% vs. 0.3%; P<0.001), schizophrenia/paranoia (1.6% vs. 5.4%; P<0.01), personality disorder (0% vs. 2.4%; P=0.003)
(Collacott et al., 1996)	Cross-sectional: 360 DS, < 35 years: 164 (45.6%); ≥ 35 yrs: 196 (55.4%) 1829 ID of other aetiologies	DAS	Compared to intellectual disabilities of other aetiologies, DS showed a reduced prevalence of absconson, aggression, antisocial behaviour, attention-seeking, excessive activity, disturbing others at night, property destruction, self-injury and untruthfulness.
(McCarthy & Boyd, 2001)	Longitudinal: 52 DS followed from childhood to adulthood. Adulthood: 28♂/52, 26.6 ± 3.45 yrs	ABI, ABS Part 1, PAS-ADD	Adulthood: 7/52 (13%) mood disorder, 5/52 (10%) phobia, 1/52 (2%) PDD, 34/52 (65%) no psychiatric disorder
(Urv et al., 2003)	Longitudinal: 529 ID: ♂48%, 56.8 ± 14.9 yrs - 202 DS / 327 non-DS	ABS Part I and II	Three year follow-up: persons without significant functional decline had stable patterns of maladaptive behaviour over time. Among those with regression in adaptive behaviour: obnoxious behaviour, lack of boundaries and overestimation of own abilities significantly increased before, and withdrawal and emotional instability coincided with, adaptive decline.
(Mantry et al., 2006)	Baseline: 186 DS: 91♂/186, 41.1 ± 11.8 yrs Longitudinal follow-up (2 yrs): 134 DS: 65♂/134, 43 ± 11.6 yrs	C21st Health Check, PAS-ADD, PPS-LD, VABS	Affective disorder (baseline: 2.7%, follow-up 2 years: 5.2%), anxiety disorder (2.7%, 1.5%), eating disorder (0%, 0%), problem behaviour (10.2%, 3.7%) and psychotic disorder (0%, 0%)
(van Gamen-Oosterom et al., 2013)	Cross-sectional: 322 DS, 170♂/322, 18.3 ± 0.82 yrs; 2076 non-DS, non-ID children, aged 15-18 yrs	CBCL, SRZ	Compared to the control group, DS presented a significantly increased total score for problem behaviour and significantly more internalizing problems (withdrawal, somatic complaints), social problems (e.g. age-appropriate behaviour and dependence on adults), attention problems (e.g. concentration, impulsiveness and being too active) and thought problems (e.g. obsessive thoughts, weird behaviour and repetitive acts)
(Straccia et al., 2014)	Cross-sectional: 34 DS, 18♂/34, 39.4 ± 8.62 yrs; 34 nonspecific ID, 19♂/34, 38.8 ± 10.67 yrs	RSMB, DBC-A, QCS	Exclusion of subjects with clinical suspicion of dementia. Compared to controls, DS scored significantly lower on mental illness (RSMB global score and subscales for avoidant disorder, psychosis and behavioural signs of depression), behavioural problems (DBC-A global score and subscales for aggressive/disruptive, self-absorbed and depressive behaviour) and higher on social behaviour (QCS).
(Makary et al., 2014)	Cross-sectional: 26 DS, 17♂/26, 26.7 ± 7.62 yrs Longitudinal: 28 DS, 15♂/28, 33.3 ± 10.84 yrs	DBC-A	No significant association between age and the number or severity of DBC-A items, taking gender, comorbid medical conditions and level of ID into account as covariates. Demented DS subjects were excluded.

<sup>†</sup>Table 4 only lists studies that assessed a variety of behaviour; those focusing on single behavioural items are only discussed in the text. ABI, Additional Behavioural Inventory; CBCL, Child Behaviour Checklist; DBC-A, Developmental Behaviour Checklist Adult version; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases and Related Health Problems; ID, intellectual disability; PAS-ADD, Psychiatric Assessment Schedule for Adults with a Developmental Disability; PPS-LD, Present Psychiatric State for adults with Learning Disabilities; QCS, Social Behaviour Questionnaire; RSMB, Reiss Screen for Maladaptive Behaviour; SRZ, Social Competence rating scale.



