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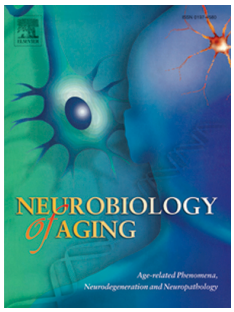

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Frontal-subcortical behaviours during Alzheimer's disease in individuals with Down syndrome

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Abstract

There is evidence that frontal-subcortical circuits play an important role in the initial presentation of dementia in Down syndrome (DS), including changes in behaviour, a decline in working memory and executive dysfunction. We evaluated 92 individuals with DS (≥ 30 years of age), divided into three groups by diagnosis—stable cognition, prodromal dementia and Alzheimer's disease (AD). Each individual was evaluated with an executive protocol developed for people with intellectual disabilities and was rated for behaviours related to frontal lobe dysfunction (disinhibition, executive dysfunction and apathy) by an informant using the Frontal Systems Behavior Scale (FrSBe). Informant-reported behaviours related to frontal lobe dysfunction were found to correlate negatively with executive function performance. Disinhibition and executive dysfunction were associated with the clinical stage of dementia. The odds of having AD increased in parallel with increases in the domain and total FrSBe scores ($p \leq 0.5$). Disinhibition, executive dysfunction and apathy should be taken into consideration during the clinical evaluation of adults with DS, and future studies should consider the intersection of neuropathology, brain connectivity and behaviour.

Keywords:

Alzheimer's disease

Down syndrome

Disinhibition

Executive dysfunction

Apathy

Dementia

1. Introduction

Down syndrome (DS) is associated with premature development of the neuropathology typical of Alzheimer's disease (AD), including early amyloid burden (senile plaques) and neurotoxic neurofibrillary tangles (Holland and Oliver, 1995; Wisniewski et al., 1985; Zigman, 2013). Although a deficit in episodic memory appears to be the main early characteristic of AD in the general population, behavioural symptoms typically appear later in the course of dementia (Gregory and Hodges, 1996; Sperling et al., 2010). In adults with DS and AD, the symptomatology at the onset of dementia has been described as atypical (Adams and Oliver, 2010; Ball et al., 2006; Deb et al., 2001; Nelson et al., 2001). It is not clear however if this is due to the "camouflage" provided by pre-existing cognitive deficit or if it is due to abnormalities related to the DS-specific brain phenotype (Holland et al., 1998). Studies suggest that, in individuals with DS, typical symptoms of frontal lobe dysfunction, such as behavioural changes (disinhibition, executive dysfunction and apathy) appear as an early manifestation prior to the appearance of short-term memory impairment, which is the characteristic early feature of AD (Ball et al., 2006; Deb et al., 2001; Dekker et al., 2018; Fonseca et al., 2016; Oliver et al., 2011).

The frontal lobe is responsible for the interconnections between the major sensory and motor systems of the brain, integrating the components necessary for human behaviour (Goldberg and Bougakov, 2005). Neuropsychological aspects related to the frontal lobe include executive functions (such as planning, inhibitory control, working memory and abstract thinking), attention and behaviour. In a recent study, our group found that behaviours related to frontal lobe dysfunction are already present (i.e. before age-related cognitive decline or the development of AD) during adulthood in ageing individuals with DS and stable cognition, and that these

behaviours can have an impact on the initial presentation of AD in DS population (Fonseca et al., unpublished results). There is evidence that neuropsychological performance related to prefrontal lobe function is most often affected in adults with DS and AD, resulting in declines in executive function (Adams and Oliver, 2010; Ball et al., 2008) and working memory (Ghezzo et al., 2014; Nelson et al., 2001; Oliver et al., 1998). Also, a recent study involving a large sample of adults with DS found that those with prodromal dementia performed significantly worse than those with preclinical dementia on cognitive outcomes related to executive function and attention, along with those pertaining memory domains (Firth et al., 2018; Startin et al., 2018). Given the few studies involving pre-clinical symptoms in people with DS, researchers emphasize the importance of developing criteria for defining prodromal dementia, early dementia, and their distinction in adults with intellectual disabilities (Krinsky-McHale and Silverman, 2013; Silverman et al., 2013).

In individuals with DS, behaviours related to frontal lobe dysfunction can be present throughout life, because of the pre-existing frontal lobe hypoplasia and poor development of regions with projections to and from neurons of the prefrontal cortex (Powell et al., 2014; Raz et al., 1995; Wang et al., 1992). In such individuals, positron emission tomography with Pittsburgh compound B (Klunk et al., 2004) indicated brain deposition of β-amyloid to occur first in the striatum, followed by the pre-frontal and anterior cingulate cortices, and it subsequently spreads to other regions of the brain (Annus et al., 2016). That early striatal pattern of cerebral amyloidosis is like what is seen in the autosomal dominant familial forms of AD (Cohen et al., 2018; Shinohara et al., 2014), which has led some researchers to hypothesise that it is related to early overproduction and/or abnormal clearance of amyloid (Annus et al., 2016; Cohen et al., 2018). In individuals with sporadic AD, senile plaques in the

striatum appear very late in the course of the disease (Braak and Braak, 1990; Cohen et al., 2018). Apart from the early striatal deposition and the consequent hypothesised effect on fronto-striatal pathways, in general the distribution of brain amyloid deposition in individuals with DS appears to be consistent with that observed in individuals with sporadic or familial AD (Bateman et al., 2012; Klunk et al., 2004). Recent evidence suggests that amyloid accumulation may be a potential biomarker for cognitive decline in adults with DS in the prodromal phase of AD (Hartley et al., 2017). It is known that frontal circuits connect the regions of the frontal cortex to the striatum, globus pallidus, substantia nigra and thalamus (Mega and Cummings, 1994). One recent study suggested that the myelination process in the frontal pathways is particularly vulnerable to ageing in individuals with DS (Powell et al., 2014), and the breakdown of late-stage myelin might be related to the subsequent amyloid deposition associated with AD (Bartzokis, 2011, 2004).

Three major frontal-subcortical circuits have been associated with major neuropsychiatric manifestations (Cummings, 1995). The first originates in the dorsolateral prefrontal cortex and is related to executive dysfunction. The second is the orbitofrontal cortex circuit, which is linked to disinhibition and obsessive-compulsive symptoms. Cognitive impairment associated with the orbitofrontal circuit may be observed in tasks involving emotional decision-making and behavioural inhibition (Bechara et al.,1994). The last is the anterior cingulate circuit and is associated with a lack of motivation or apathy, error correction and response inhibition (Tekin and Cummings, 2002). Disruption at any point in any of the three frontal-subcortical circuits (including striatal regions, basal ganglia, and thalamus) may result in changes in behaviour and executive dysfunction (Tekin and Cummings, 2002).

The Frontal Systems Behavior Scale (FrSBe), devised by Grace and Malloy (2001), is a questionnaire designed specifically to evaluate behaviours related to frontal lobe dysfunction (namely executive dysfunction, disinhibition and apathy) that compares the current and past behaviour of an individual. The FrSBe has been used in studies of various types of dementia, including AD (Malloy et al., 2007; Peavy et al., 2013; Ready et al., 2003; Stout et al., 2003). Higher FrSBe scores translate to less adapted behaviour. In a study investigating the neuropsychiatric features of frontal lobe dysfunction in autopsy-confirmed AD, frontally mediated behaviours, as assessed by the FrSBe, were found to have been affected early in the progression to AD. However, only a few studies have investigated the relationship between the expression of frontally mediated behaviours and dementia in DS (Adams and Oliver, 2010; Ball et al., 2010, 2008). To our knowledge, this is the first study to use a specific behaviour rating scale for the assessment of disturbances associated with frontal-subcortical brain circuits in individuals with DS. The objectives of this study were to examine the relationship between frontally mediated behaviours and executive functions and to determine whether the FrSBe score indicates the clinical diagnosis of prodromal dementia and AD in individuals with DS.

2. Methods

2.1. Study sample

In the study we included 92 individuals with DS, all of whom were ≥ 30 years of age (mean: 42.4 years; standard deviation: 8.4 years; range 30–64 years). Of the 92 individuals evaluated, 58 (63%) were males. All individuals met the criteria for a diagnosis of DS, as established in the International Classification of Diseases, 10th revision (ICD-10; code, Q90). Individuals were recruited from among those currently

or previously enrolled in programs for adults with intellectual disability offered by the Association of Parents and Friends of Individuals with Intellectual Disability of Sao Paulo or the Association for the Holistic Development of Individuals with Down Syndrome, as well as from among individuals who became aware of the study and demonstrated an interest in participating. The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas* and was registered with the National Committee for Ethics in Research through the *Plataforma Brasil* (CAAE no. 37381414.8.0000.0065). For all of the individuals included, the objectives of the study were explained in a simple, concrete manner, and any questions or concerns they had were addressed. Written informed consent was obtained not only from the individuals with DS but also from their legal guardians. Assessments were performed in sound-proof rooms arranged for the evaluation, either at the Institute of Psychiatry of the University of São Paulo School of Medicine *Hospital das Clínicas* or at one of the Associations involved.

2.2. Clinical assessment and diagnosis

All individuals with DS underwent dementia assessment with the Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) informant questionnaire (Ball et al., 2004), an instrument adapted for use specifically in adults with DS that considers deterioration from the best level of functioning and has been validated for use in Brazil (Fonseca et al., in press). Data supplement 1 describes all the informant-based measures used. All of the informants were closely related to the participant, with whom they had been in daily contact for at least ten years. The informant questionnaire was conducted by a psychiatrist trained in the use of the instrument and

with knowledge of the specificities of DS. As part of the CAMDEX-DS questionnaire, information on current use of medications, living arrangements, relationship with informants, duration of contact, education and employment were investigated. For subsequent analysis the medication variable was dichotomised and considered "yes" whenever participants were taking medication considered to affect the central nervous system, modulating the effects of neurotransmition (e.g. antipsychotic, antidepressant, mood stabilizer, acetylcholinesterase inhibitor, anticonvulsant, antiparkisonian agent, and stimulants) with no determination concerning effects of any single medication. Besides these variables, the clinical anamnesis also included the investigation on family history of AD and sedentary life according to the informant report.

The clinical evaluation of dementia was based on the criteria established in the CAMDEX-DS, the ICD-10 (World Health Organization, 2004) and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (American Psychiatric Association, 2013) and was performed by an evaluator who was blinded to the results of the neuropsychological assessment and to those of the other instruments. The individuals were divided into three diagnostic categories: stable cognition, prodromal dementia and AD. Prodromal dementia was defined as an intermediate group of probable early dementia in which the cognitive or functional decline was superior to that expected for non-pathological ageing but not severe enough to meet the criteria for a diagnosis of dementia.

2.3. Behaviours related to frontal lobe dysfunction

For measures of neuropsychiatric manifestations related to the frontal-subcortical circuits, all informants completed the FrSBe (Grace and Malloy, 2001; Siviero et al.,

2003), which provides scores for executive dysfunction, disinhibition and apathy domains, from which a total score is derived. The scale compares the past and current behaviours of the individual. For the present analysis we considered only the current behaviour scores. The FrSBe was applied by a psychiatrist trained in the use of the instrument, with knowledge of the specificities of DS and blinded to the clinical evaluations performed with the CAMDEX-DS. The FrSBe has been validated for use in different types of dementia, having been shown to discriminate well between AD and frontotemporal dementia (FTD) and to be useful in assessing the three frontal syndromes, in isolation or in combination (Malloy et al., 2007; Stout et al., 2003). To our knowledge, the FrSBe has never before been used in the assessment of behaviours related to frontal lobe dysfunction in individuals with DS.

2.4. Level of intellectual disability

Premorbid severity of intellectual disability was defined by a psychiatrist through analysis of the maximum level of individual adaptive behaviour achieved throughout life using a background information anamnesis according to the American Association on Intellectual and Developmental Disabilities framework (AAIDD, 2010) and the results of a neuropsychological assessment of intellectual functioning using the Wechsler Abbreviated Scale of Intelligence (WASI [Wechsler, 1999]) that had been performed before there was any sign of cognitive decline. The psychiatrist was blinded to the CAMDEX-DS results and other neuropsychological evaluations. The level of intellectual disability was categorised by ICD-10 code: F70 (mild intellectual disability); F71 (moderate intellectual disability); F72 (severe intellectual disability); F73 (profound intellectual disability); and F79 (unspecified intellectual disability) when it was difficult to reach a consensus on the degree of disability

because of the presence of cognitive decline and a lack of information regarding the history of the individual.

2.5. Neuropsychological assessment

A neuropsychologist with experience in DS and intellectual disability performed the neuropsychological assessment, which consisted in the administration of the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS), as described by Ball et al. (2004); the Wechsler Abbreviated Scale of Intelligence (WASI [Wechsler, 1999]); and a executive protocol devised by Ball et al. (2008).

The CAMCOG-DS is the neuropsychological section of the CAMDEX-DS and contains subscales for the following domains: orientation; language (comprehension and expression); memory (new learning, remote and recent); attention; praxis (drawing of complex figures and ability to carry out complex tasks); abstract thinking; and perception. As in a previous study of individuals with DS and AD (Ball et al., 2006), the CAMCOG-DS performance specifically related to frontal lobe function was analysed as a composite domain, designated “EF and attention”, which combines the scores for verbal fluency, attention-calculation, clock drawing and abstract thinking.

The WASI, adapted and validated for use in Brazil (Trentini et al, 2014), was applied in its reduced version, with the Vocabulary and Block Design subtests, providing an estimated intelligence quotient, which facilitated the definition of intellectual disability for individuals who showed no signs of cognitive decline. For cases of dementia or suspected cognitive decline, we considered cognitive assessments performed prior to the cognitive decline, if available.

For the neuropsychological evaluation of executive functions, we used a protocol designed specifically for individuals with DS, developed by researchers at the University of Cambridge (Ball et al., 2008) and used in previous studies in the area (Adams and Oliver, 2010; Annus et al., 2016; Ball et al., 2008). In addition to six tasks related to executive function (CAMCOG-DS fluency item, Cats and dogs- a task based on day-night stroop (Gerstadt et al., 1994), Spatial reversal- based on procedure used by McEvoy et al. (1993), Weigl sorting (Grant and Berg 1948), Tower of London (Shallice, 1982), Scrambled boxes (Griffith et al., 1999)), the protocol includes two tasks related to executive memory (Prospective memory- the "remembering to belong" subtest of the Rivermead Behavioural Memory Test for Children (Wilson et al., 1991), and Object memory from the battery of neuropsychological tests employed by Oliver et al. (1998) in the identification of cognitive impairment. Test content, modifications and administration are described in Ball et al. (2008). Data supplement 1 shows all the neuropsychological measures applied and cognitive processes assessed.

2.6. Statistical analysis

For the sample as a whole and for each diagnostic group (stable cognition, prodromal dementia and AD), descriptive analyses of the demographic variables are presented as absolute and relative frequencies or as means and standard deviations. Between-group differences were assessed with Kruskal-Wallis test for continuous variables and with Fisher's exact test for categorical variables for which the number of cases was less than five for one or more variable; for all other categorical variables, between-group differences were assessed with Pearson's chi-square test. Spearman's rho coefficient was used in order to establish the correlation between the total FrSBe

score and the cognitive performance of the individual. Multiple linear regressions were conducted in order to determine whether the total FrSBe scores and the cognitive performance test results varied among the three different diagnostic groups. The total FrSBe scores and the cognitive performance scores were selected as the primary outcome of interest. To assess the strength of the association of the diagnostic group with the total FrSBe score and with cognitive performance, all linear regression models were adjusted for age, gender, type of education, degree of intellectual disability, and current use of medications affecting the central nervous system. In addition, to determine the degree to which informant reports of behaviours related to frontal lobe dysfunction were predictive of the diagnosis, we created three dichotomous variables (AD versus prodromal dementia, AD versus stable cognition and prodromal dementia versus stable cognition). We performed multiple logistic regression analyses, assigning those dichotomous variables as the dependent variables (primary outcomes) and each of the total FrSBe scores as the independent (predictor) variables, including age, gender, degree of intellectual disability and current use of medications affecting the central nervous system as covariates. The level of statistical significance was set at 5%. All selected data were tabulated with the Research Electronic Data Capture program (Harris et al., 2009), and the analyses were carried out using the SPSS Statistics software package, version 24.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Demographic and clinical data

The demographic characteristics of the sample are shown in Table 1. Of the 92 individuals evaluated, 62 (67.4%) were classified as having stable cognition, 17

(18.5%) were classified as having prodromal dementia and 13 were classified as having AD (14.1%). During the evaluation period, 48 (52.2%) of the individuals had hypothyroidism and all those individuals were receiving effective treatment. Twenty (21.7%) of the 92 individuals were using medications that affect the central nervous system: eight were using an antipsychotic; nine were using an antidepressant; four were using a mood stabiliser; two were using an acetylcholinesterase inhibitor; one was using an anticonvulsant; and one was using an antiparkinsonian agent. Of those 20 individuals, 14 were using one such medication and six were using two.

There were significant differences among the diagnostic groups for the variables age, family history of AD, use of medication affecting the central nervous system, sedentary lifestyle, living arrangements, relation to the informant and duration of contact with the informant. On average, those in the prodromal dementia and AD groups were older than were those in the stable cognition group. Individuals with AD tended to use more medications affecting the central nervous system. In addition, the individuals with AD were most likely to have a family history of AD and to have a sedentary lifestyle, whereas the individuals in the prodromal dementia group presented results for those two variables that were intermediate between the results obtained for the other two groups. In comparison with the individuals in the stable cognition and prodromal dementia groups, those in the AD group were more likely to live in a nursing home and less likely to live at home with relative, as well as being more likely to have a caregiver than a parent as their informant. For the relation to the informant, the prodromal dementia group presented a result intermediate between that of the AD group and that of the stable cognition group. The mean duration of contact between the informant and the individual with DS was longer in the AD group than in the stable cognition group. However, the AD group showed a larger standard

deviation for that variable and was therefore statistically similar to the two other groups, whereas the stable cognition and prodromal dementia groups differed significantly from each other.

TABLE 1 HERE

3.2. Relationship between behaviours related to frontal lobe dysfunction and diagnostic status

Table 2 shows the associations between the informant reports of behaviours related to frontal lobe dysfunction and the various diagnoses, adjusted for age, gender, type of education, degree of intellectual disability and use of medications affecting the central nervous system. Executive dysfunction showed a clear association with the diagnostic group, even when adjusted for the other variables. In terms of the frequency of disinhibition, there was a clear distinction between the stable cognition and prodromal dementia groups, although the difference in relation to the AD group was linked to the adjustment variables. Without adjustment for age, gender, type of education, degree of intellectual disability and medication use, there were significant differences among the groups for all of the items ($p < 0.05$ for all).

Within the stable cognition group, we identified four individuals with higher (outlier) FrSBe scores for apathy. As the total FrSBe score involves the sum of the FrSBe domain scores, we performed both analyses: with the whole sample and excluding those four individuals from our analysis of apathy and total FrSBe. As can be seen in Table 4, after excluding the outliers, we also found a difference for the total FrSBe score, although the difference for apathy continued to be modelled by all adjusted variables.

TABLE 2 HERE

3.3. Relationship between behaviours related to frontal lobe dysfunction and cognitive performance

Six participants did not perform direct cognitive assessment. Three due to advanced stage of dementia, two due to inability in expressive language (no speech), and one because he refused to continue the cognitive assessment even though he maintained his consent for all other evaluations. Table 3 shows the correlation between the informant-reported scores for the FrSBe items and the performance of the individuals on the cognitive tasks (N=86). With the exception of one of the items analysed (correlation of disinhibition and verbal fluency), all cognitive tasks were shown to have some association with all three of the behaviours related to frontal lobe dysfunction investigated and with the total FrSBe score, either considering the executive protocol devised by Ball et al. (2008) or the CAMCOG-DS executive function and attention tasks. Cognitive performance correlated most strongly with the executive dysfunction domain, the total FrSBe score and the apathy domain, in that order.

TABLE 3 HERE

3.4. Relationship between executive performance and diagnostic status

Analysis of the association between the diagnostic status and performance on cognitive tasks related to executive function showed that, when adjusted for age, gender, type of education, degree of intellectual disability and use of medication affecting the central nervous system, half of the tasks proposed in the study protocol had a significant association with the diagnosis (Table 4). The cognitive tasks that were most strongly associated with diagnosis status were Cats and Dogs, Weigl

Sorting, Tower of London and Prospective Memory, as well as the combined score for all of the executive tests of the protocol. However, for the Weigl Sorting and Tower of London tasks, the association was strong only in relation to a diagnosis of prodromal dementia. On all four of those tasks, the individuals diagnosed with dementia scored very close to the minimum (floor effect). When not adjusted for age, gender, type of education, intellectual disability and medication, all of the tasks had a *p*-value below 0.05, which shows that the adjustment variables had a strong influence on executive performance. For the executive function and attention tasks of the CAMCOG-DS, those variables also influenced the cognitive performance, although it was not possible to establish a direct association with the diagnosis, despite the fact that the score diverged widely among the groups. Data supplement 2 shows the number of individuals with floor and ceiling scores on individual tasks for each of the diagnostic groups.

TABLE 4 HERE

3.5. Impact of behaviours related to frontal lobe dysfunction on the diagnostic status

As can be seen in Table 5, the odds of being diagnosed with AD increased in parallel with increases in the specific total FrSBe score. The data in the table show by how much a one-point increase in that specific score increases the chance of each given diagnosis over the previous (less severe) one. When we compared the prodromal dementia and stable cognition groups, we found a greater number of FrSBe items for which higher scores increased the chance of that individual to be diagnosed with prodromal dementia, namely disinhibition, executive dysfunction and the total FrSBe score. The executive dysfunction and total FrSBe scores were found to be predictors of a diagnosis of AD, whereas the apathy score was found to be a predictor

of a diagnosis of prodromal dementia. When we excluded the outlier values for the apathy and total FrSBe scores (for the four individuals in the stable cognition group), apathy was found to be a predictor of a diagnosis of prodromal dementia over stable cognition (odds ratio = 1.087; p = 0.026). For all other analyses, exclusion of the outliers did not alter the results.

TABLE 5 HERE

4. Discussion

In our sample of adults with Down syndrome, we found that behaviours related to frontal lobe dysfunction were predictive of a diagnosis of prodromal dementia or AD. Informant reports of such behaviours were found to correlate with the performance of the individual on cognitive tasks that involve executive functions. These findings support our hypothesis that behaviours related to frontal lobe dysfunction and cognitive dysfunction in the executive domain manifest during the progression to clinical AD in adults with DS.

It is known that frontal-subcortical syndromes can reflect disruption of working memory and executive function (Cummings, 1995). In the present study, we found a correlation between the performance of individuals on executive tasks and informant reports of frontally mediated behaviours. As expected, the correlation was greater for the participants' performance with the executive domain of the informant's report. In addition, there was a significant difference between the total of the proposed executive tasks and the three clinical diagnoses, with those with AD being considered worse performing followed by those with prodromal diagnosis. In a comparison of sixteen months of follow-up, researchers found that only individuals considered in cognitive deterioration presented a decline in the measures of executive functions (Adam and Oliver, 2010). Furthermore, we identified a greater correlation of

cognitive tasks with the FrSBe domains for those tests involving working memory (e.g., Cats and dogs, Tower of London, Object memory), followed by the task involving prospective memory. Functional neuroimaging studies have correlated several regions of the frontal lobe (dorsolateral prefrontal cortex, right lateral prefrontal cortex, anterior cingulate gyrus, and medial frontal lobe) in the processes involved in working memory (Nissim et al., 2016; Burgess et al., 2001; Cabeza and Nyberg, 2000). Research also suggests that the frontal cortex would encode prospective action (Mackey and Curtis, 2017). Patients with frontal lobe lesions were particularly impaired in prospective memory tasks (Fortin et al., 2002; Cockburn, 1995). Disinhibition was the domain with the lowest correlation with the cognitive tasks in our study, although the correlation still exists with the exception of one of the cognitive tasks (verbal fluency). Lesions in this region is known to not necessarily leave obvious cognitive deficits but have a great impact on the expression of behaviour (Goldberg and Bougakov, 2005). In studies involving patients with orbitofrontal lesions, they showed impairment in decision-making despite adequate performance in traditional executive function tests (Damasio, 1996; Bechara et al, 1994). However, the evaluation of cognitive performance alone, at a single time point, is not sufficient to draw any conclusions regarding diagnosis. Although our study used cognitive tasks developed specifically for individuals with DS, the results of more than half of the tests used in our study were strongly influenced by age, gender, type of education, level of intellectual disability and use of medications affecting the central nervous system, thus precluding us from identifying any direct associations between those results and the diagnostic groups. That underscores the importance of comparing individual performance at two different time points during cognitive decline. The strong association between age and diagnostic group, together with the

strength of performance, even considering the previous level of intellectual disability; as well as the broad variability of individual cognitive performances, substantially influenced by emotional issues, empathy, mood and other subtle conditions, make it a challenge to perform a single assessment of the cognitive performance of an individual with intellectual disability. Making such an assessment as part of a neuropsychological evaluation requires specific knowledge and training in the area.

Our findings regarding the relationship between cognitive performance and diagnosis differs from that of the original executive protocol study (Ball et al., 2008), in which the AD group showed impaired performance on all cognitive tasks, even when the results were adjusted for age and degree of intellectual disability. However, methodological differences between the two studies preclude direct comparisons. First, our study included a prodromal dementia group, whereas the original protocol study compared only individuals with and without AD. Second, in addition to age, gender and degree of intellectual disability, we adjusted for type of education and the use of medications affecting the central nervous system. Our study also considered not only individuals with mild and moderate intellectual disability but also those with severe intellectual disability.

In view of our findings and defining prodromal dementia as an intermediate clinical state between stable cognition and AD, we can hypothesise that the symptoms of dementia related to frontal lobe function first appear in the prodromal phase, with an increase in disinhibition and executive dysfunction, whereas the features of apathy appear after AD has become established, all such symptoms being heightened by the progression of the disease. Another study employing the FrSBe showed that changes in behaviours related to frontal lobe dysfunction are common in the early phases of AD and during mild cognitive impairment in the general population, even before there

is any evidence of a decline in functional abilities (Ready et al., 2003). In a study using the FrSBe to discriminate between FTD and AD, increases in apathy and executive dysfunction were observed after the onset of both diseases, although only the individuals in the FTD group showed an increase in disinhibition (Malloy et al., 2007), which differs from our findings. One possible explanation for that discrepancy might be related to the behavioural phenotype of DS throughout life, a hypothesis that would need to be further investigated.. In another study employing the FrSBe, apathy and executive dysfunction were found to be prominent in all phases of AD, whereas the level of disinhibition was found to be high only in severe AD (Stout et al., 2003). Studies investigating behavioural and psychological symptoms in different forms of dementia, including AD, have shown that apathy was present in all forms and correlated with executive function (Perri et al., 2014). Our findings regarding the onset of behaviours related to frontal lobe dysfunction and their impact during the progression of the disease agree with those of a recent collaborative study, conducted by the University of Cambridge and University of São Paulo, using the CAMDEX-DS, which indicated an initial impact on executive dysfunction together with memory/orientation decline, with the appearance of disinhibited and apathetic signs throughout the dementia process (Fonseca et al., unpublished results). However, as our study had a cross-sectional design, this is a finding that could be verified only in a longitudinal follow-up study. If we compare the data obtained for our stable cognition group with those of the FrSBe normative sample (Grace and Malloy, 2001), we can see that, even when there was no evidence of cognitive decline, the executive dysfunction domain and total FrSBe scores differed by more than 10 points, in the direction of disruptive behaviour, considering the mean and standard deviation for the population with a low level of education in the 40- to 59-year age group.

Nevertheless, the differences in age and education from our sample in respect to the normative sample do not allow us to reach any conclusions, there being only a tendency toward behaviours related to frontal lobe dysfunction in the population with DS.

In our study, a number of demographic characteristics were associated with the diagnostic group. Age was strongly associated with the clinical diagnosis. For the general population, age is considered the main risk factor for the development of late-onset dementia (Vardarajan et al., 2014). For individuals with DS, there is evidence that age is a major risk factor for degenerative processes (Cole et al., 2017; Head et al., 2011; LeVine et al., 2017), such individuals showing an age-dependent increase in the prevalence of dementia symptoms (Coppus et al., 2006; Holland et al., 2000), which occur nearly two decades earlier than in the general population. In our sample, the individuals in the stable cognition group were considerable younger than were those in the prodromal dementia group, who were in turn younger than those in the AD group, similar to what has been reported for mild cognitive impairment in the general population (Petersen et al., 2014). That clear difference in age probably also influenced other variables examined in our sample, such as the relation to and duration of contact with the informant. However, it is noteworthy that the minimum duration of contact with the informant was 10 years in all three groups. We can hypothesise that the older age of the individuals in the AD group increased the likelihood that they had lost their parents and would therefore have a professional caregiver as an informant. The living arrangements might also indicate the greater need for professional support among those diagnosed with AD, who more often lived in nursing homes and less often lived at home with their parents. Further investigations are needed in order to substantiate these hypotheses. A sedentary

lifestyle and a family history of AD were also associated with the diagnosis. Nevertheless, as this was a cross-sectional study, we cannot comment on the nature of these associations.

Our study has some limitations that need to be considered. The first is the small sample size, especially in the prodromal dementia and AD groups. Another limitation is the fact that we found no instrument designed specifically to evaluate frontally mediated behaviours in individuals with DS. Some of the questions presented by the FrSBe might not be appropriate for use in that population. In addition, the behaviours related to frontal lobe dysfunction were assessed on the basis of informant reports. In some studies, the FrSBe has also been applied directly to the subjects (Batistuzzo et al., 2009; Schiehser et al., 2013). Furthermore, our study had a cross-sectional design, whereas a longitudinal analysis would make it possible to understand the evolution of the such behaviours and analyse the nature of the associations.

In conclusion, our findings indicate the importance of evaluating behaviours related to frontal lobe dysfunction during the ageing process in individuals with DS. Our initial hypothesis that executive dysfunction, disinhibition and apathy are present during the progression to dementia and that those behaviours are associated with the diagnosis, as well as with cognitive performance on tasks related to executive function, was confirmed by our analyses. There is a need for further studies including a longitudinal exploration of behaviours related to frontal lobe dysfunction in this population and involving structural and functional analysis of the brain, which could aggregate knowledge to identify the basis of the differential symptomatology of AD in this population.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Table 1
Demographics characteristics and differences among the diagnostic groups

Characteristic	Total (N = 92)	Diagnostic group: Stable cognition (n = 62)	Prodromal dementia (n = 17)	AD (n = 13)	*p*-value
Age (years), mean (SD)	42.43 (8.48)	39.69 (7.37)[a]	46.35 (5.06)[b]	50.46 (10.30)[b]	0.000[c]
Male gender, n (%)	58 (63)	39 (62.9)	9 (63)	10 (76.9)	0.465[d]
Degree of intellectual disability, n (%)					
Mild	34 (37)	28 (45.2)[a]	4 (23.5)[a,b]	2 (15.4)[b]	
Moderate	34 (37)	24 (38.7)[a]	9 (52.9)[a]	1 (7.7)[b]	
Severe	22 (23.9)	10 (16.1)[a]	4 (23.5)[a]	8 (61.5)[b]	0.000[e]
Unspecified	2 (2.2)	0[a]	0[a]	2 (15.4)[b]	
Maternal age at delivery,[f] (years), mean (SD)	34.65 (7.69)	33.78 (7.37)	34.50 (9.09)	39.25 (6.01)	0.087[c]
Family history of AD, n (%)	23 (25)	12 (19)[a]	4 (23.5)[a,b]	7 (53.8)[b]	0.036[e]
Use of medication affecting the CNS, n (%)	20 (21.7)	9 (14.5) [a]	3 (17.6) [a]	8 (61.5) [b]	0.002[e]
Sedentary lifestyle, n (%)	36 (39.1)	19 (30.6)[a]	7 (41.2)[a,b]	10 (76.9)[b]	0.007[e]
Living arrangements, n (%)					
Nursing home	3 (3.3)	0[a]	0[a,b]	3 (23.1)[b]	
Sheltered accommodation/assisted living	1 (1.1)	0[a]	0[a]	1 (7.7)[a]	0.002[d]
Home with relative	84 (91.3)	59 (95.2)[a]	17 (100)[a]	8 (61.5)[b]	
Own home/home with a partner	4 (4.3)	3 (4.8)[a]	0[a]	1 (7.7)[a]	
Relation to the informant, n (%)					
Parent	52 (56.5)	41 (66.1)[a]	8 (47.1)[a,b]	3 (23.1)[b]	
Sibling or other relative	38 (41.3)	21 (33.9)[a]	9 (52.9)[a]	8 (61.5)[a]	0.004[d]
Caregiver or other	2 (2.2)	0[a]	4 (16.7)[a,b]	2 (15.4)[b]	
Duration of contact (years), mean (SD)	41.92 (9.28)	39.74 (7.56)[a]	45.83 (5.51)[b]	47.23 (15.69)[a,b]	0.003[c]
Education, n (%)					
None	25 (27.2)	13 (21)	8 (47.1)	4 (30.8)	0.457[d]

Special school	39 (42.4)	27 (43.5)	6 (35.3)	6 (46.2)	
Special class in a mainstream school	4 (4.3)	3 (4.8)	1 (5.9)	0	
Mainstream school	24 (26.1)	19 (30.6)	2 (11.8)	3 (23.1)	
Employed,[g] n (%)	26 (28.6)	21 (34.4)	2 (11.8)	3 (23.1)	0.181[d]

Key: AD, Alzheimer's disease; CNS, central nervous system.
[a,b] Groups differ when $p < 0.05$.
[c] Kruskal-Wallis test.
[d] Fisher's exact test.
[e] Pearson's chi-square test.
[f] N=89 (no data for three individuals).
[g] N=91 (no data for one individual).

Table 2
Frontal Systems Behavior Scale scores and differences among the diagnostic groups

		Diagnostic group			
	Total	Stable cognition	Prodromal dementia	AD	
	(N = 92)	(n = 62)	(n = 17)	(n = 13)	
FrSBe score (min–max)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*-value[a]
Apathy domain (14–70)					
All data	28.70 (14.13)	23.70 (9.42)	29.41 (11.37)	51.61 (13.88)	0.686
Outliers[b] excluded		22.01 (6.98)			0.382
Disinhibition domain (15–75)					
All data	24.40 (5.85)	22.51 (4.74)[c]	27.58 (4.96)[d]	29.23 (7.39)[c,d]	0.016
Executive dysfunction domain (17–85)					
All data	43.75 (13.21)	38.80 (11.58)[c]	49.58 (9.87)[d]	59.69 (7.89)[d]	0.025
Total (46–230)					
All data	96.85 (28.88)	85.03 (21.90)	106.58 (20.57)[d]	140.53 (19.93)[d]	0.059
Outliers[b] excluded		82.27 (19.37)[c]			0.024

Key: AD, Alzheimer's disease; FrSBe, Frontal Systems Behavior Scale.
[a] Linear regression, adjusted for age, genderm type of education, intellectual disability and use of medications affecting the central nervous system.
[b] Values for four of the individuals in the stable cognition group were excluded.
[c,d] Groups differ when $p < 0.05$.

Table 3
Correlation between the informant-reported Frontal Systems Behavior Scale score and performance on the cognitive tasks of the executive protocol devised by Ball et al. (2008)

	Current FrSBe score			
	Apathy domain	Disinhibition domain	Executive dysfunction domain	Total
Executive protocol scores	Spearman's rho	Spearman's rho	Spearman's rho	Spearman's rho
Cognitive tasks				
Executive function				
Verbal Fluency	−0.380[a]	−0.191	−0.373[a]	−0.381[a]
Cats and Dogs	−0.450[a]	−0.395[a]	−0.533[a]	−0.539[a]
Spatial Reversal	−0.350[a]	−0.282[a]	−0.481[a]	−0.446[a]
Weigl Sorting	−0.335[a]	−0.377[a]	−0.515[a]	−0.499[a]
Tower of London	−0.436[a]	−0.313[a]	−0.530[a]	−0.521[a]
Scrambled Boxes	−0.408[a]	−0.327[a]	−0.465[a]	−0.482[a]
Executive memory				
Prospective Memory	−0.330[a]	−0.407[a]	−0.505[a]	−0.474[a]
Object Memory	−0.488[a]	−0.433[a]	−0.540[a]	−0.550[a]
Total executive function	−0.492[a]	−0.429[a]	−0.623[a]	−0.612[a]
CAMCOG-DS executive function and attention domain	−0.430[a]	−0.388[a]	−0.497[a]	−0.522[a]

Key: FrSBe, Frontal Systems Behavior Scale; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down Syndrome.
[a]$p \leq 0.01$.

Table 4
Cognitive performance on the cognitive tasks of the executive protocol devised by Ball et al. (2008) and differences among the diagnostic groups

		Diagnostic group			
	Total (N=86*)	Stable Cognition (N=60)	Prodromal dementia (N=16)	AD (N=10)	
Executive protocol scores (min–max)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*-value [a]
Cognitive tasks					
Executive function					
Verbal Fluency (0–5)	1.97 (0.99)	2.17 (0.92)	2.00 (0.81)	0.70 (0.82)	0.515
Cats and Dogs (0–16)	9.08 (6.21)	11.22 (5.27)[b]	6.06 (5.61)[c]	1.10 (3.47)[c]	0.012
Spatial Reversal (0–7)	3.23 (2.82)	3.85 (2.69)	2.56 (2.78)	0.60 (1.89)	0.476
Weigl sorting (0–5)	1.64 (1.89)	2.20 (1.94)[b]	0.56 (1.09)[c]	0.00 (0.00)[b,c]	0.015
Tower of London (0–12)	4.49 (3.80)	5.68 (3.63)[b]	2.63 (2.94)[c]	0.30 (0.94)[b,c]	0.019
Scrambled Boxes (0–11)	7.35 (3.16)	8.07 (2.91)	7.38 (1.99)	3.00 (2.86)	0.662
Executive memory					
Prospective Memory (0–4)	2.12 (1.49)	2.68 (1.20)[b]	1.06 (1.52)[c]	0.40 (0.51)[c]	0.001
Object Memory (0–10)	6.42 (3.28)	7.50 (2.57)	5.38 (3.07)	1.60 (2.67)	0.252
Total executive function	36.29 (18.64)	43.36 (15.47)[b]	27.62 (11.91)[c]	7.7 (10.05)[d]	0.013
CAMCOG-DS executive function and attention domain	9.93 (5.31)	11.15 (4.92)	10 (4.38)	2.5 (2.22)	0.584

Key: AD, Alzheimer's disease; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down Syndrome.
[*] six individuals did not take part in the neuropsychological assessment
[a] Linear regression, adjusted for age, gender, type of education, intellectual disability and use of medications affecting the central nervous system.
[b,c,d] Groups differ when $p < 0.05$.

Table 5
Impact of the Frontal Systems Behavior Scale score on the odds of a clinical diagnosis, adjusted for age, gender, type of education, level of intellectual disability and use of medications affecting the central nervous system

Comparison	Odds ratio	95% CI	*p*-value
Prodromal dementia vs. stable cognition			
Disinhibition	1.222	1.060–1.408	0.006
Executive dysfunction	1.091	1.022–1.164	0.009
Total FrSBe	1.046	1.013–1.081	0.007
AD vs. prodromal dementia			
Apathy	1.166	1.009–1.348	0.037
AD vs. stable cognition			
Executive dysfunction	1.121	1.000–1.257	0.050
Total FrSBe	1.120	1.024–1.225	0.013

Key: FrSBe, Frontal Systems Behavior Scale.

Highlights

- Disinhibition, executive dysfunction and apathy are predictive of a diagnosis of AD
- Behaviours related to frontal lobe correlates with executive function performance
- Behaviours related to frontal lobe dysfunction manifest during AD progression in DS
- Frontal-subcortical behaviours should be taken into consideration during evaluation