Multidimensional apathy in behavioural variant frontotemporal dementia, primary progressive aphasia and Alzheimer's disease

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Abstract

Apathy is prevalent in dementia, such as behavioural variant frontotemporal dementia (bvFTD), primary progressive aphasia (PPA) and Alzheimer's disease (AD). As a multidimensional construct, it can be assessed and subsumed under a Dimensional Apathy Framework. A consistent apathy profile in bvFTD and PPA has yet to be established. The aim was to explore apathy profiles and awareness in bvFTD, PPA and AD. 12 bvFTD, 12 PPA, 28 AD patients and 20 matched controls, as well as their informants/carers, were recruited. All participants completed the Dimensional Apathy Scale (DAS), assessing Executive, Emotional and Initiation apathy subtypes, a one-dimensional apathy measure, depression measure, functional and cognitive screens. Apathy subtype awareness was determined through DAS informant/carer- and self-ratings discrepancy. Apathy profile comparison showed bvFTD patients had significantly higher Emotional apathy than AD patients ($p < .01$) and significantly higher apathy over all subtypes than PPA patients (p's < .05). Additionally, bvFTD patients had significantly lower awareness for Emotional apathy ($p < .01$) when compared to AD and PPA patients. All patient groups had significant global apathy over all subtypes compared to controls. The emergent apathy profile for bvFTD seems to be Emotional apathy (indifference or emotional/affective neutrality), with lower self-awareness in this subtype. Further, lower self-awareness for Executive apathy (lack of motivation for planning, organisation or attention) differentiates bvFTD from PPA. Future research should investigate the cognitive and neural correlates as well as the practical impact of apathy subtypes.

Introduction

Apathy as a lack of motivation is frequently observed in dementia, occurring in up to 90% of patients with Frontotemporal dementia (FTD)[1] and Alzheimer's disease (AD).[2] FTD is a umbrella term for behavioural variant FTD (bvFTD) and Primary Progressive Aphasia, which can be further subdivided into semantic dementia (SD), progressive non-fluent aphasia (PNFA) and logopenic variant PPA (lvPPA). In terms of FTD, research has shown that bvFTD patients have higher levels of apathy compared to PPA patients.[3,4] The impact of demotivation is widespread in these diseases, being associated with problems in activities of daily living, decreased quality of life and increased caregiver burden.[5-8]

Apathy is composed of different subtypes[9-11] with certain multidimensional models focusing on cortical and subcortical brain network dysfunction. Levy and Dubois proposed a prefrontal cortex-basal ganglia neuroanatomical apathy model composed of Auto-Activation apathy (e.g. impairments of self-generation), Cognitive apathy/inertia (e.g. impairment of goal-management, use of strategy and planning) and Emotional apathy (e.g. impairment of emotional processing).[10,11] Apathy subtypes can further be subsumed under the Dimensional Apathy Framework, which is a cumulative model taking in to account previous subtypes of apathy inclusive of the Levy and Dubois model.[12] This is a three-dimensional model of apathy comprising Executive, Emotional and Initiation apathy subtypes with self-awareness or insight interacting with each subtype. Executive apathy is a lack of motivation towards planning, organisation or attention; Emotional apathy is an indifference, emotional/affective neutrality, blunting or flatness; and Initiation apathy is lack of motivation for self-generation of thought or actions. While several tools measure elements of this framework[12], the Dimensional

Apathy Scale (DAS)[13] directly measures these subtypes. Previous research has shown different profiles of apathy in motor neurone disease[14,15] and Parkinson's disease.[15,17] Additionally, the apathy profile in AD has been characterised by increased Executive, Emotional and Initiation subtypes, with decreased awareness, or insight, restricted to Executive and Initiation Subtypes.[18] More recent research using the DAS has found differing apathy profiles with higher Emotional apathy in bvFTD when compared to AD and higher Executive apathy in AD when compared to bvFTD.[19] However, the profile of apathy and self-awareness of demotivation has not been explored in PPA and bvFTD.

Other research using different tools, such as the apathy subscale questions of the Neuropsychiatric Inventory[20], found that certain characteristics of apathy differentiate FTD from AD, where FTD showed a decreased emotional output, lack of initiative or lack of interest towards friends or family.[21,22] More recently, when compared to AD patients, bvFTD have been observed to have decreased self-awareness relating to apathy as well as increased apathy in emotional domains on the Lille Apathy Rating Scale (LARS).[23] Another study looking at apathy characteristics derived from various functional (Disability Assessment for Dementia Scale; DAD)[24] and behavioural scales (Cambridge Behaviour Inventory-Revised; CBI-R)[25] found prominent affective-emotional apathy characteristics (i.e. the inability to use emotional context for guidance of behaviour) in bvFTD, while both AD and bvFTD displayed cognitive apathy characteristics (i.e. demotivation for participation in goal-directed behaviour).[26] However, these aforementioned tools were designed as general behaviour measures, therefore being non-specific to apathy subtypes with only a few multidimensional apathy tools, e.g. Dimensional Apathy Scale[13] and LARS, [27] currently validated for use in dementia. To build upon this research, it is timely to determine the apathy profile based on a

structured framework such as the Dimensional Apathy Framework and using multidimensional apathy tools such as the DAS, within dementia diagnosis of bvFTD, PPA and AD.

The aim was to explore the apathy profile and awareness of apathy subtypes in bvFTD and PPA in comparison to AD and determine any relationships to cognitive functioning and activities of daily living.

Methods

Participants

12 PPA patients, 12 bvFTD patients and 28 AD patients, as well as their carers/relatives/close friends, were recruited from a Specialist Early Onset Dementia Research Clinic (the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register; CDC-DART), at the Anne Rowling Regenerative Neurology Clinic, University of Edinburgh. The PPA patient group was composed of 9 lvPPA, 2 PNFA patients and 1 SD patient. All patients fulfilled consensus clinical diagnostic criteria for each disease.[28-30] Diagnoses were made following multi-disciplinary clinical assessments (neurology, psychiatry, neuropsychology), which included neuropsychological assessment of domains such as executive, language, memory and visuospatial functioning and behaviour. Cerebrospinal fluid biomarkers and neuroimaging was incorporated where appropriate to support the diagnostic process. 20 healthy controls and their informants were recruited from the University of Edinburgh Departmental Volunteer Panel. Exclusion criteria for participants was severe diabetes, epilepsy, alcohol/substance-related disorders, severe head injury (that required intensive care hospitalization), traumatic brain injury (inclusive of subarachnoid haemorrhage) and other present or

past significant comorbid medical illness (such as stroke, psychiatric disease etc.). Controls were not specifically assessed for cognitive impairment (i.e. using Addenbrooke's Cognitive Examination III or other measures) in the present study, although were excluded if information on the University of Edinburgh Departmental Volunteer Panel database indicated cognitive impairment.

Ethical approval was obtained from the National Health Service (NHS) South East Scotland Research Ethics Committee 02 and the School Philosophy, Psychology and Language Sciences (PPLS) Ethical Committee. All patient, control, informant and carer participants gave informed consent following the Declaration of Helsinki.

Procedures

Patients (and their carers/relatives/close friends) and controls (and their informants) were asked to complete measures of apathy and depression. Carers/relatives/close friends and informants completed apathy, depression and activities of daily living measures about their observations of the patients and controls, so as to account for problems with awareness or insight.

Measures

The Dimensional Apathy Scale (DAS)[13-14] was used to assess multidimensional apathy, through 3 subscales: Executive apathy, Emotional apathy and Initiation apathy. It is composed of 24 items which are scored on a 4 point Likert response scale. Each 8 item subscale has a minimum of 0 (least apathy) and maximum of 24 (most apathy). The total score can range from 0 to 72. The DAS has been validated for use in dementia.[18] Previously published cut-offs were used for each subscale.[14] The cutoff of ≥14 was used

for presence of Executive apathy, ≥15 was used for presence of Emotional apathy and ≥16 was used for presence of Initiation apathy. Both self-rated and informant/carer-rated DAS data was collected.

The Apathy Evaluations Scale (AES)[31] was used as a gold-standard to assess one-dimensional apathy. It is composed of 18 items which are scored on a 4 point Likert response scale. The scale ranges from a minimum of 0 (least apathy) to a maximum of 72 (most apathy). The AES has been validated in dementia, and an abnormality cutoff of >41.5 (carer-rated version) was used.[32] The informant-rated version was utilised.

The Geriatric Depression Scale – Short Form (GDS-15)[33] was used to screen for depression. It is a 15 item scale that is scored dichotomously (Yes/No). The results range from a minimum of 0 (not depressed) to a maximum of 15 (most depressed). The cutoff of >6 was used presence of depressive symptoms.[34] The informant-rated version was utilised.

Please see supplementary materials for correlations between the AES, DAS and GDS-15 in the patient sample.

The Lawton Instrumental Activities of Daily Living (LIADL)[35] assessment was used to assess functional independence of the patients. It is an 8-item carer-rated assessment, with total scores ranging from 0 (low function, dependent) to 8 (high function, independent).

The Addenbrooke's Cognitive Examination III (ACE-III)[36] and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[37] were used to examine global cognitive functioning and behaviour change of patients.

Statistical analysis

R software[38] and SPSS statistics was used to perform all analysis. Shapiro Wilk tests were used to examine distribution of the data to determine use of parametric or non-parametric analysis. Descriptive data (Clinical and demographic variables) were compared using Analysis of Variance (ANOVA), with follow-up post hoc t-test. Informant/carer-rated versions of AES and GDS-15 were used for comparison. Gender distribution was compared using Chi Squared.

A 4 x 3 mixed analysis of variance (ANOVA) was used to compare groups (bvFTD vs PPA/lvPPA Only vs AD vs control) on each informant/carer-rated DAS Subscale (Executive vs Emotional vs Initiation) with post hoc t-tests (Holm Correction). Additionally, a further 4 x 3 mixed analysis of variance (ANOVA) was used to compare groups (bvFTD vs PPA/lvPPA Only vs AD vs control) on awareness discrepancy on different DAS Subscales (Executive vs Emotional vs Initiation) with post hoc t-tests (Holm Correction). Awareness discrepancy on apathy subtypes was determined by calculating the difference between informant/carer-rated DAS scores and self-rated DAS scores. Power was calculated using the partial eta squared (ηp^2) and Cohen's *d*. Chi Squared analysis was used for comparison of frequency of apathy impairment (number of participants above cutoffs) for each patient group. The subsampled lvPPA only group (N=9) was used in addition to of the whole PPA group (N = 12) for additional analysis. Correlational analysis was conducted using Spearman's Rho (Holm corrected).

Results

Descriptive

Table 1. Clinical and demographic variables for patients and controls

	lvPPA Only (N = 9)	PPA (N = 12)	bvFTD (N = 12)	AD (N = 28)	Control (N = 20)	F / χ^2 Value	*p*-value
Age (Mean, S.D.)	62.8 (7.5)	63.2 (6.7)	61.0 (11.9)	62.5 (5.6)	64.9 (9.6)	F = 0.603	n.s.
Gender (M/F)	6/3	7/5	8/4	16/12	12/8	χ^2 = 0.328	n.s.
Years of Education (Mean, S.D.)	17.0 (4.8)††††	15.6 (4.7)†	12.2 (3.7)†	13.4 (3.0)††	14.7 (2.7)	F = 2.451	n.s.
AES (Mean, S.D.) / 72	42.2 (13.1)	41.3 (12.1)	55.3 (9.5)	42.9 (9.3)	27.7 (5.9)	F = 24.828	< .001
GDS-15 (Mean, S.D) / 15	11.7 (5.4)	5.9 (5.5)	5.0 (2.3	6.5 (4.3)	1.9 (2.0)	F = 6.524	< .001
Age Onset (Mean, S.D.)	61.0 (6.0)††††	58.3 (6.9)†††	52.1 (11.9)‡	57.9 (6.3)‡‡		F = 2.035	n.s.
Disease Duration (Median, IQR)	4 (1.5)††††	5 (1.75)†††	5 (7)‡	5 (4)‡‡		F = 2.102	n.s.
ACE-III Total (Mean, S.D.) / 100	62.9 (26.0)	66.3 (24.2)‡‡‡	71.4 (14.5)†	65.2 (15.8)		F = 0.472	n.s.
ECAS Cognitive Total (Mean, S.D) / 136	61.8 (35.9)	67.2 (34.9)	72.3 (22.0)‡	72.5 (21.1) ‡‡‡‡		F = 0.157	n.s.
ECAS Behaviour domain (Median, IQR) / 5	3 (3)	2 (3.5)†	5 (3)‡	2 (1.5)‡‡‡‡		F = 6.305	< .01
LIADL Total (Mean, S.D.) / 8	6.1 (1.4)	6.5 (1.4)	3.2 (1.5)	5.1 (2.0)		F = 10.949	< .001

lvPPA = Logopenic Variant Primary Progressive Aphasia; PPA = Primary Progressive Aphasia; bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's disease; n.s. = not significant; S.D. = Standard Deviation; IQR = Interquartile Range; LIADL = Lawton Instrumental Activities of Daily Living; ACE-III = Addenbrooke's Cognitive Examination III; ECAS = Edinburgh Cognitive and Behaviour ALS Screen; AES = Apathy Evaluation Scale; GDS-15 = Geriatric Depression Scale- Short Form

† N=11; †† N=22; ††† =10; †††† =7; ††††† =8; ‡ N=9; ‡‡ N=27; ‡‡‡ N=12; ‡‡‡‡ =15

Note. Comparison is between PPA, bvFTD, AD and Controls. lvPPA Only group is a subsample from the PPA group.

The most common carer or informant relationship to patients and controls was spouse (71%), followed by other relative (21%) and other (8%), such as close friends. Table 1 shows there was no significant difference between patient groups (bvFTD, PPA and AD) and controls on age, years of education and gender distribution (see Table 1).

In comparing bvFTD, PPA and AD groups on clinical variables, there was no significant difference between age of onset and disease duration (see Table 1). Post hoc tests showed that all patient groups were significantly more apathetic on the AES than controls (PPA vs Controls: t(30)=-4.269, p<0.001; bvFTD vs Control: t(30)=-10.277, p<0.001, AD vs Control: t(46)=-6.434., p<0.001). Post hoc tests showed bvFTD patients were significantly more apathetic on the AES than AD (t(38)=-3.862, p<0.001) and PPA (t(22)=3.202, p<0.01), with no significant difference between PPA and AD. 57.1% of AD (N = 16), 83.3% of bvFTD (N = 10) and 66.7% of PPA (N = 8) patients were above cutoff on the AES, but this was not significantly different. 66.7% of the lvPPA patients (N = 6), 50.0% of the PNFA patients (N = 1) and the SD patient were apathetic based on the AES. No controls were above cutoffs for apathy, based on the AES.

In terms of depression, post hoc tests showed patient groups were significantly more depressed than controls (PPA vs Controls: t(30)=-3.563, p<0.01; bvFTD vs Control: t(30)=-3.370, p<0.01, AD vs Control: t(46)=-4.498, p<0.001). There was no significant difference between patients on depression levels. 21.4% of AD (N = 6), 25.0% of bvFTD (N = 3) and 25.0% of PPA (N = 3) patients showed above cutoff depressive symptoms on the GDS, but this was not significant. 44.4% of the lvPPA patients (N = 4) were above cutoff for depression based on the GDS-15. The SD patient and none of the PNFA

patients were above cutoff for depression, based on the GDS-15. No controls were above cutoffs for depression, based on the GDS-15.

Further, there was a significant difference on the LIADL between all patient groups with bvFTD patients being significantly more functionally impaired than both AD ($t(38)=3.037$, $p<0.01$) and PPA ($t(22)=-5.606$, $p<0.001$), as well as AD being significantly more functionally impaired than PPA ($t(38)=-2.220$, $p<0.05$). However, there were no significant correlations between AES and LAIDL in any patient groups, showing no relationship between one dimensional apathy and function. There were no significant correlations between the AES and cognitive functioning (ACE-III and ECAS). Additionally, there was a significant difference on the ECAS behaviour domains. bvFTD had significantly more behaviour change than AD ($t(22)=-3.773$, $p<0.01$) and PPA ($t(18)=2.569$, $p<0.05$).

Apathy profile comparison

Using previously published DAS subscale cutoff scores[14] to examine frequency of impairment, 75.0% bvFTD patients (N = 9) were impaired on Emotional apathy, which was significantly higher ($\chi^2(2, N = 52)=8.73$, $p<.05$) when compared to 25.0% of AD patients (N = 7) and 41.7% of PPA patients (N = 5). There was no significant difference on frequency of impairment on Executive apathy between bvFTD (83.3%, N = 10), PPA (41.7%, N = 5) and AD (50.0%, N = 14). There was no significant difference on frequency of impairment on Initiation apathy between bvFTD (83.3%, N = 10), PPA (50.0%, N = 6) and AD (67.9%, N = 19). Subdividing the PPA group, the SD patient, 50.0% of the PNFA patients (N = 1) and 44.4% of the lvPPA patients (N = 4) were impaired on Initiation apathy. The SD patient, both PNFA patients and 22.2% of the

lvPPA patients (N = 2) were impaired on Emotional apathy. The SD patient and 33.3% of the lvPPA (N = 3) were impaired on Executive apathy, with the PNFA patients being unimpaired.

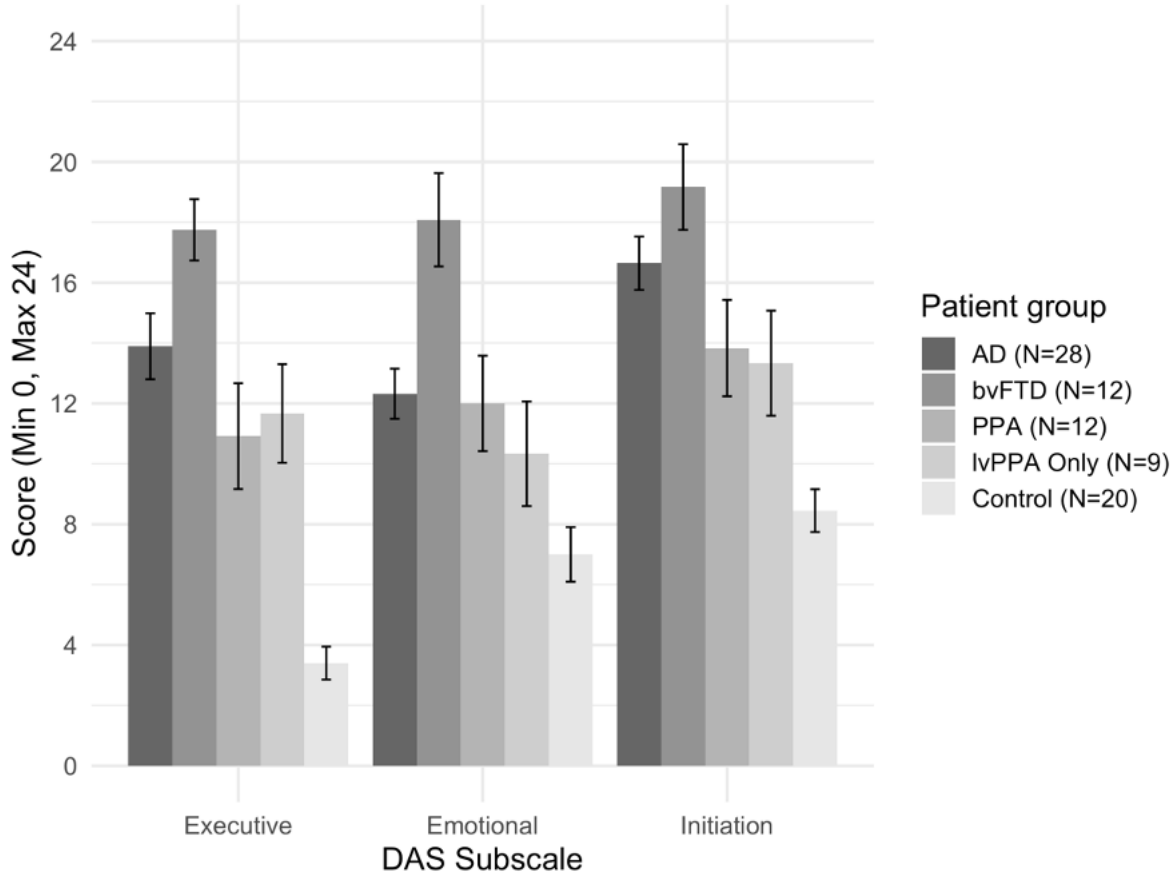

Figure 1. Apathy subtype profile (informant/carer-ratings) for AD, bvFTD, PPA (including the lvPPA Only group) and controls.

Higher score indicates higher apathy. Standard Error bars shown.

Note: lvPPA Only group is a subsample from the PPA group

Figure 1 presents the comparison between patient groups (bvFTD vs PPA vs AD vs Controls) on the informant/carer-rated DAS subscales. There was a significant main effect for group ($F(3,68)=33.357$, $p<0.001$, $\eta p^2= 0.595$), main effect of DAS subscale ($F(2,136)=11.548$, $p<0.05$, $\eta p^2= 0.145$) and significant group vs DAS subscale

interaction (F(6,136)=2.373, $p<0.05$, $\eta p^2= 0.095$), showing overall differential apathy profile (DAS subscale scores) between and within patient groups. Inter-group post hoc tests showed that only bvFTD patients had significantly higher Emotional apathy than AD patients (t(38)=-3.562, $p<0.01$, $d = 1.23$), with no difference on Executive ($d = 0.74$) and Initiation ($d = 0.53$) apathy. Further bvFTD had significantly higher apathy over all apathy subtypes when compared to PPA patients (Executive: t(22)=3.375, $p<0.01$, $d = 1.23$; Emotional: t(22)=2.752, $p<0.05$, $d = 1.02$; Initiation: t(22)=2.499, $p<0.05$, $d = 1.02$). There was no significant difference between AD and PPA patients on DAS subscales (Executive: $d = 0.51$; Emotional: $d = 0.07$; Initiation: $d = 0.56$). When compared to controls, global apathy over all subtypes was observed in bvFTD patients (Executive: t(30)=-13.640, $p<0.001$, $d = 4.98$; Emotional: t(30)=-6.650, $p<0.001$, $d = 2.43$; Initiation: t(30)=-7.523, $p<0.001$, $d = 2.74$), PPA patients (Executive: t(30)=-4.955, $p<0.001$, $d = 1.81$; Emotional: t(30)=-2.965, $p<0.05$, $d = 1.08$; Initiation: t(30)=-3.519, $p<0.01$, $d = 1.28$) and AD patients (Executive: t(46)=-7.628, $p<0.001$, $d = 2.23$; Emotional: t(46)=-4.279, $p<0.001$, $d = 1.25$; Initiation: t(46)=-6.790, $p<0.001$, $d = 1.99$).

Analysis using the lvPPA only group (in place of the PPA group) showed similar pattern of apathy profile results, with a significant main effect for group (F(3,65)=34.724, $p<0.001$, $\eta p^2= 0.616$), main effect of DAS subscale (F(2,130)=10.564, $p<0.05$, $\eta p^2= 0.140$) and significant group vs DAS subscale interaction (F(6,136)=2.771, $p<0.05$, $\eta p^2= 0.113$), showing overall differential apathy profiles (DAS subscale scores) between and within patient groups. Post hoc tests showed that lvPPA only had significantly higher Executive apathy than controls (t(30)=-6.130, $p<0.05$, $d = 2.46$) with no differences on Emotional ($d = 0.76$) and Initiation apathy ($d = 1.26$). bvFTD patients had significantly higher apathy than lvPPA over all DAS subtypes (Executive: t(19)=3.319, $p<0.01$, $d =$

1.46; Emotional: t(19)=3.325, p<0.01, d = 1.46; Initiation: t(19)=2.622, p<0.05, d = 1.16). There was no significant difference between lvPPA and AD patients on DAS subscales (Executive: d = 0.40; Emotional: d = 0.43; Initiation: d = 0.69).

In terms of function, there were no significant correlations between any DAS subscales and the ECAS, ACE-III or LIADL.

Apathy subtype awareness

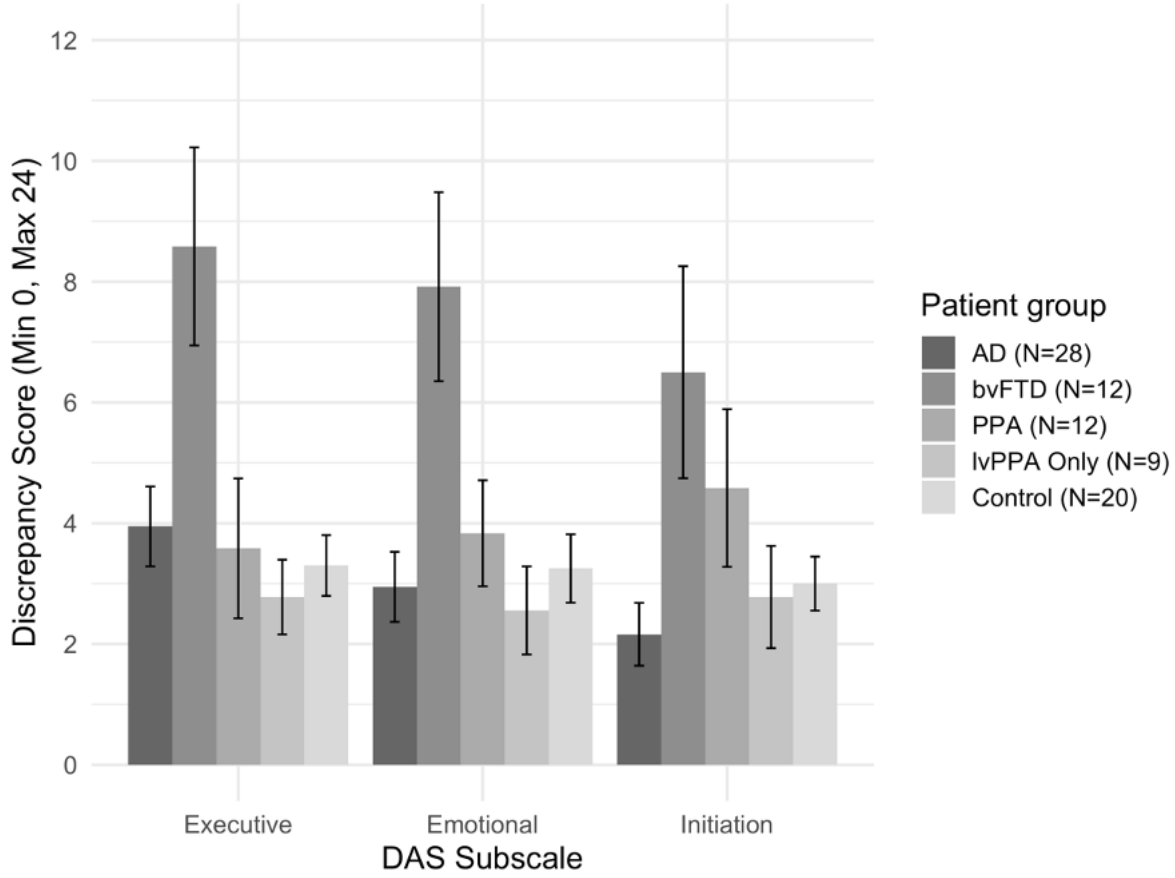

Figure 2. Apathy subtype awareness profile (difference between self-ratings and informant/carer-ratings) for AD, bvFTD, PPA (including the lvPPA Only group) and controls.

Higher discrepancy score indicates less awareness. Standard Error bars shown.
Note: lvPPA Only group is a subsample from the PPA group

There was only a significant main effect for group ($F(3,68)=6.505$, $p<0.01$, $\eta p^2= 0.223$), showing an overall difference on the awareness discrepancy score between groups (see Figure 2). Inter-group post hoc tests showed that bvFTD were found to have significantly less awareness for Emotional apathy when compared to AD patients ($t(38)=-4.315$, $p<0.001$, $d = 1.49$) and PPA patients ($t(22)=2.277$, $p<0.05$, $d = 0.93$). There was no significant difference for Initiation apathy awareness between bvFTD and AD ($d = 0.72$) or PPA ($d = 0.36$). Additionally, bvFTD patients were observed to only have significantly less awareness of Executive apathy when compared to PPA patients ($t(22)=2.491$, $p<0.05$, $d = 1.02$). When compared to controls, only bvFTD had significantly less awareness over all apathy subtypes (Executive: $t(30)=-3.731$, $p<0.01$, $d = 1.31$; Emotional: $t(30)=-3.320$, $p<0.01$, $d = 1.21$; Initiation: $t(30)=-2.389$, $p<0.05$, $d = 0.83$). There was no significant difference between PPA and controls on apathy subtype awareness (Executive: $d = 1.81$; Emotional: $d = 1.08$; Initiation: $d = 1.29$). There was no significant difference between AD and controls on apathy subtype awareness (Executive: $d = 0.62$; Emotional: $d = 0.27$; Initiation: $d = 0.11$).

Analysis using the lvPPA only group (in place of the PPA group) showed a main effect of group ($F(3,65)=8.356$, $p<0.001$, $\eta p^2= 0.278$), showing a between group difference on DAS subscales. Post hoc tests showed that bvFTD had significantly less awareness compared to lvPPA for Executive ($t(19)=-2.934$, $p<0.05$, $d = 1.29$) and Emotional ($t(19)=-2.789$, $p<0.05$, $d = 1.23$) apathy, with no difference on Initiation apathy ($d = 0.76$). There were no differences between lvPPA and AD on apathy subtype awareness (Executive: $d = 0.73$; Emotional: $d = 0.01$ Initiation: $d = 0.16$). There were no significant differences between lvPPA and controls on apathy subtype awareness (Executive: $d = 0.24$; Emotional: $d = 0.29$; Initiation: $d = 0.10$).

Discussion

The findings show that it is important to understand apathy profiles in different dementia subtypes. Apathy subtype profiles using the DAS can be used to differentiate bvFTD from PPA and AD. Specifically, Emotional apathy (as indifference, emotional/affective neutrality, blunting or flatness) was the distinguishing apathy subtype for bvFTD compared to other dementias. Further, bvFTD showed less awareness of Emotional apathy overall. In comparison to PPA, bvFTD patients showed global apathy over all subtypes, additionally supplemented by less awareness of Executive apathy (lack of motivation for planning, organising and attention) and less awareness of Emotional apathy. While bvFTD showed most apathy overall, global apathy was observed in all dementia diagnosis, when compared to controls. All these results are further supported by a similar pattern of difference on the one-dimensional apathy measure (AES), with bvFTD displaying the most apathy compared to other dementias (PPA and AD) and controls. This suggests that inter-dementia comparisons using the DAS allows for breaking down components of apathy and may hold more value in identifying specific apathy subtype profiles.

With 75% of bvFTD patients displaying Emotional apathy based on previously published cutoffs[14], this showcases the prominence of this subtype relative to controls and other dementias. This is further supported by previous research using specific and non-specific apathy subtype measures showing these emotional apathy characteristics are key in bvFTD. [19,21-23,26] Previous research using the LARS showed bvFTD displayed greater impairment of emotional apathy and self-awareness domains in comparison with AD.[23] Emotional apathy could indeed be said to overlap contextually with loss of sympathy and empathy, which is a defining feature of bvFTD.[28] Further, bvFTD patients

have been observed to have impairments in emotional recognition and social cognition.[39-42] In bvFTD, empathy and social cognition deficits were associated with atrophy to orbitofrontal areas, medial prefrontal cortex and amygdala.[43-45] These areas overlap with the Emotional-affective apathy subtype[10,11] which is akin to the Emotional apathy subtype of the Dimensional Apathy Framework.[12] The cognitive-neuroanatomical-motivational overlap for Emotional apathy could be explained by impairment in discrete processes of Behavioural/emotional self-regulation, which mediate motivational, emotional and social aspects of behaviour.[12,46] The high degree of conceptual overlap between empathy, social cognition and Emotional apathy points towards a need for further comprehensive examination of the mechanistic relationship between these factors.

Within dementia syndromes, lower awareness of Emotional Apathy may be distinguishing characteristic for bvFTD and that an additional lower Executive apathy awareness differentiates bvFTD from PPA. This study overall reaffirms that awareness of apathy subtypes is a key factors for defining apathy subtype profiles for different dementias. Previous research has shown widespread loss of insight relative to other cognitive and behavioral symptoms, inclusive of emotional insight[47-49], which may be an extension of the Emotional apathy reduction in self-awareness. As such, awareness of apathy could be used to diagnostically differentiate dementia syndromes, particularly bvFTD from AD and PPA, and clinicians could therefore work with families/caregivers to improve understanding of this. Through measuring this by the discrepancy between self-ratings and informant/carer-ratings on DAS apathy subtypes, a more representative view of awareness and impairments associated with it can be produced. Our finding is supported by previous research showing bvFTD patient's self-awareness

deficit in combination with emotional apathy differed from patients with AD, albeit originally being assessed by individual questions rather than a discrepancy score.[23] As such self-awareness through individual questions may be paradoxical as answering questions about oneself implies a certain level of awareness. This is further compounded by apathy being associated with anosognosia[50] further influencing self-ratings. Of note, there was no significant difference between dementia syndromes on Initiation apathy awareness or on scores on the Initiation apathy subscale. This could be accounted for by the lack of differentiation of dementia syndromes on the Initiation apathy profile scores, which has been previously observed when comparing bvFTD and AD.[19] How apathy subtype awareness changes as disease progresses and its interaction with cognitive functioning should be further explored, with an aim to understand the practical impact of these subtypes.

While this provides a foundation for apathy profile research in FTD, this study would merit larger scale replication. Additionally, while imaging biomarkers or cerebrospinal biomarkers were used to support diagnosis, there was no specific data available, which would be beneficial for understanding apathy profiles. Furthermore, while PPA patients were observed to have global apathy relative to controls, there were no differences in comparison to AD. This could be accounted for by the majority of the PPA group being composed of lvPPA, which overlap with AD pathology.[51] Based on frequency of impairment on the DAS, lvPPA group had a mixed apathy profile, with a lower occurrence of Emotional apathy, which could be accounted for by the lack of difference in relation to this subtype when compared to controls. The one SD patient showed global apathy over all subtypes (Executive, Emotional and Initiation). Both the PNFA patients showed Emotional apathy (with one showing additional Initiation apathy), and

no Executive apathy. However, due to small sample size of PPA group, future larger scale research should aim to elucidate apathy profiles of PNFA, SD and lvPPA patient groups. Further, the lack of association between cognitive functioning, activities of daily living and apathy (AES) is contraindicative of findings from previous research.[7,8] Previous research has found that certain deficits in emotional recognition are associated with Emotional apathy and deficits in intrinsic response generation is associated with Initiation apathy in motor neuron disease.[52] Additional research should also explore the underlying cognitive processes and their association with particular apathy subtypes in dementia. Further, due to sample size constraints, it was not feasible to explore the impact of apathy subtypes on these practical variables. Future research should explore the practical elements of living with specific apathy profiles in various dementia syndromes to build on functional elements of the Dimensional Apathy Framework.

To conclude, while bvFTD patients displayed the highest levels of apathy over all subtypes, Emotional apathy seems to be consistently characteristic in terms of bvFTD, when compared to AD, PPA and controls. Further to this, supplementary decreased awareness for apathy subtypes were observed to be variable in dementia syndromes, with bvFTD patients displaying less awareness of their Emotional apathy and also less awareness of Executive apathy (compared only to PPA). This shows the robust application of the Dimensional Apathy Framework within dementia for differentiating apathy subtype profiles. It supports the importance of routine evaluation to further clinical understanding of motivation in neurodegenerative disease. Future research should utilise the Dimensional Apathy Framework to explore neural, as well as cognitive and functional, correlates of apathy subtypes and their practical impact in

dementia and other neurodegenerative diseases. This will help inform person-centred interventions through better profiling and therefore mediation or management of demotivational problems.

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Declaration of Conflicting Interests

None.

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Supplementary Table 1. Correlations in whole dementia group (bvFTD, PPA and AD) of DAS subscales, AES and GDS-15 in dementia group (N=52)

	AES	GDS-15	DAS Executive	DAS Emotional	DAS Initiation
AES	1.000	0.643***	0.830***	0.623***	0.878***
GDS-15	-	1.000	0.618***	0.270*	0.560***
DAS Executive	-	-	1.000	0.545***	0.787***
DAS Emotional	-	-	-	1.000	0.567***
DAS Initiation	-	-	-	-	1.000

PPA = Primary Progressive Aphasia; bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's disease; AES = Apathy Evaluation Scale; GDS-15 = Geriatric Depression Scale- Short Form; DAS = Dimensional Apathy Scale

$p < 0.05$*; $p < 0.01$**; $p < 0.001$***