THE GREEK VERSION OF THE DIMENSIONAL APATHY SCALE: PSYCHOMETRIC PROPERTIES AND CLINICAL UTILITY IN AMYOTROPHIC LATERAL SCLEROSIS

Abstract

Background. Apathy is the most common behavioral symptom of amyotrophic lateral sclerosis (ALS). However, previous research assessed apathy as a unidimensional construct and part of ALS behavioral changes and used scales that were not specifically designed to assess patients with motor disability.

Aim. To explore the internal consistency and construct validity of the Dimensional Apathy Scale in Greek speaking population, evaluate its clinical utility in identifying apathy and its dimensions in patients with ALS and serving as a prognostic factor in their carers' burden.

Method. One hundred healthy participants and fourteen non-demented ALS patients and their carers were included. The Dimensional Apathy Scale (DAS) was used to evaluate patients' emotional, executive and initiation dimensions of apathy rater either by the patient or the carer. Additional standardized behavioral scales were also administered. Furthermore, patients' cognitive and mood status was also evaluated using standardized scales. Carers' burden was assessed with the Zarit Burden Inventory (ZBI) scale.

Results. The psychometric properties (internal consistency and construct validity) of the DAS in Greek population were found to be good. We found that 70% of ALS patients showed apathy based on the DAS total score and that compared to healthy group they showed significantly higher apathy in all examined dimensions. Assessment of apathy dimensions between patient and carer did not reveal differences. Regression analysis within carers showed that when considering ALS clinical, cognitive and mood status, as well as patients' apathy dimensions rated by the patient and the carer, patients' emotional apathy as rated by the carer emerged as the single significant predictor of carers' burden.

Conclusion. The Greek version of DAS is a reliable and valid scale for measuring apathy and its subtypes in ALS. From a clinical point of view, not only we identified apathy in 70% of non-demented ALS patients but also observed that patients' emotional apathy as rated by their carers is the single most significant prognostic factor for carers' burden. Based on the latter and considering that apathy is a major risk factor for morbidity and mortality in ALS, future multidisciplinary interventions are necessary to educate both patients and their carers.

Introduction

Apathy, which is defined by lack of motivation to goal-directed behaviors and may be a sign of different neurodegenerative and psychiatric diseases (Chase., 2011, Marin., 1996,), is the most common behavioral symptom in patients with amyotrophic lateral sclerosis (ALS), being observed in 30-60% of patients (Caga et al., 2016, Chio et al., 2010, Radakovic et al., 2015, Santangelo et al., 2017). It is regarded as one of the extra-motor ALS symptoms (Goldstein & Abrahams, 2013) and is associated with atrophy in both dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) (Tsujimoto et al., 2011).

Previews research on apathy mostly relied on questionnaires that generally detect behavioral deficits and evaluate apathy as a unidimensional symptom (e.g. Cambridge Behavioural Inventory revised [CBI], Wear et al., 2008). However, apathy is not a unidimensional symptom but refers to a multidimensional construct that consists of three dimensions, that is the emotional, the executive and the initiation one (Marin, 1991, Radakovic et al., 2015). The emotional subtype is associated with emotional understanding, the executive subtype is associated with organization and planning, while the initiation subtype is associated with behavioral initiatives, either cognition or act (Radakovic et al., 2015). In addition to the use of non-specific for apathy questionnaires and others that use a unidirectional approach, other assessment tools measuring apathy included statements about physical activity (e.g. Frontal Systems Behavior Scale [FrSBe], Grace & Malloy, 2001). As a result, scores were influenced by the ALS-characteristics muscular weakness and thus any accurate distinction between the impaired motor skills symptoms and those of apathy was hard to be made (Bock et al., 2016, Burke et al., 2015, Caga et al., 2016, Chio et al., 2010, Lillo et al., 2012, Watermeyert et al., 2015,). It was only recently that a multidimensional approach towards the evaluation of apathy was taken into consideration (i.e. Dimensional Apathy Scale [DAS], Radakovic et al., 2015) enabling a more delineate examination of apathy dimension in ALS, as well as other neurodegenerative diseases (Radakovic et al., 2017).

Nevertheless, the evaluation of apathy in ALS is of primary importance. This is because it is associated with poor disease prognosis and worse patient's motor dysfunction (Burke et al., 2017, Caga et al., 2016) as well as with the quality of life and the presence of bulbar symptoms (Chio et al., 2010). Also, apathy may co-occur with cognitive dysfunction, particularly with executive deficits, considering the common neuroanatomical substrate of cognitive and behavioral extra-motor impairment in ALS (Andrews et al., 2016).

Due to the progressive attenuation of the disease, patients are increasingly dependent on their carers (Krivickas et al., 1997). The carers' burden is often very high, and it is a subject

of debate what factors relate to and how they affect it (Lillo et al., 2012). Carers are directly or indirectly affected by this debilitating disease, not only due to patients' physical and motor-related changes (Baxter et al., 2013, Brulleti et al., 2014, Gauthier et al., 2007, Pagnini et al., 2010, Watermeyer et al., 2015) but also cognitive symptoms (Burke et al., 2015, Pagnini et al., 2010, Bock et al., 2016). ALS-related behavioral changes affect the burden of ALS carers (Abrahams et al., 2013, Bock et al., 2016, Chio et al., 2010, Pagnini et al., 2010, Merrilees et al., 2010, Tremolizzo et al., 2016, Watermeyer et al., 2015) and apathy constitutes an important prognostic indicator for carers' burden and depression (Burke et al., 2015, Chio et al., 2010).

The aim of the present study is to examine the psychometric properties of the DAS in Greek speaking population and further investigate its clinical utility in detecting apathy in non-demented patients with ALS and identifying its prognostic role in their carers' burden.

Method

Participants

One hundred healthy volunteer participants of both genders were included as a control group. Fourteen non-demented ALS patients and their carers were also included. All patients underwent clinical assessment, including full neurological and electrophysiological examination, and diagnosed with sporadic ALS (definite, probable, laboratory supported, possible) according to the modified El Escorial diagnostic criteria for ALS (Brooks et al., 2000).

Inclusion criteria for the present study were the following: (a) absence of a history of any neurologic conditions affecting cognition (other than ALS for patients); (b) no serious psychiatric disease (e.g., major depression, schizophrenia); (c) no family history of ALS or other known neurodegenerative disease; (d) absence of psychoactive drugs or other medication that could affect mental status; and (e) absence of dementia [Mini Mental State Examination >25; preserved activities of daily living, social and personal conduct and insight based on patient's and carer's self-reports]. Patient's disease disability level was evaluated using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Gordon et al. 2010). All healthy participants, ALS patients and their carers provided inform consent for the study, which was approved by the ethical committee of our institution.

Psychometric examination

Apathy scale

Dimensional Apathy Scale (DAS): Apathy was measured using the DAS (Radakovic et al., 2015). It is a multidimensional construction including assessing of the three subscales of apathy (emotional/executive/initiation). It is composed of 24 items with four possible answers: almost always, often, occasionally, hardly ever on a 4-point Likert type scale. It is completed both from patient (patient DAS – pDAS) and from informant/carer (informant DAS – iDAS). The iDAS form was administered to HC and carers, according to previous studies. The DAS yields three subscales scores and a total score of 72. The scores are ranging from 0 to 72 and higher scores indicate most apathy and minimum least apathy. The original version of the scale was adapted to the Greek language following the translation-back translation method. Specifically, the original English version was translated to the Greek language by a native Greek speaker being fluent in English, then translated back to English by a native Greek speaker being also fluent in English and finally checked by one of the authors of the original version of the DAS.

Other psychometric scales

Frontal Behavioral Inventory (FBI): Behavioral disturbances in ALS were measured using the FBI (Kertesz et al., 1997, Aretouli et al., 2006). It is a 24-item questionnaire assessing behavioral changes. At the end of each question the carer is asked about behavioral changes and scores according to the following conventional scale: 0 = none, 1 = mild/occasional, 2 = moderate, 3 = severe/most of the time. The FBI yields a total score ranging between 0-72 with higher scores being indicative of greater/more often behavioral changes, as well as a negative behavioral score based on FBI items between 1-12 and a disinhibition score based on FBI items between of 13-24.

ALS Depression Inventory (ADI): Depressive symptoms were measured using the ADI (Kubler et al., 2005, Ferentinos et al., 2011). It is a self-report screening questionnaire for depressive disorders and is specifically designed for the patients with neurodegenerative diseases (Kubler et al,.2005). It consists of 12 suggestions with 4 possible answers: agree fully, agree, disagree, disagree fully on a 4-point Likert type scale. The scores are ranging from 0 (best possible) to 48 (worst possible) with scores between 22 and 28 indicating mild depression.

Cognition

Edinburgh Cognitive and Behavioral ALS Screen (ECAS): All patients administered the ECAS scale (Abrahams et al., 2014; Kourtesis, 2018). ECAS is a multidomain brief assessment of cognitive functions that are typically affected (ALS-Specific: Fluency, Executive Functions, Language Functions) as well as cognitive functions that are not typically affected in ALS but are common in disorders of older adults (ALS Non-specific: Memory, Visuospatial Functions). A total ECAS score as well as subscores for ALS-specific and ALS-non-specific are calculated. In addition, the ECAS includes a brief evaluation of patient's behavioral changes and psychotic symptoms based on informant/carer semi-structured interview.

Caregiver's burden and depression scales

Zarit Burden Inventory (ZBI): Carers' burden was assessed using the ZBI (Zarit, Reever et al., 1980, Papastavrou et al., 2006), a self-report questionnaire completed from carer, that included 22 items with a total score ranging from 0 (no burden) to 88 (high burden). A total score of ≥24 is considered as a cut-off score for the presence of significant burden (Burke et al., 2015, Schreiner et al., 2006).

Center for Epidemiologic Depression Scale Revised (CES-D): Depressive symptoms of carers were measured using the CES-D (Radloff., 1977, Fountoulakis et al., 2001). It is a screening scale for depressive symptoms and consists of 20 suggestions with four possible answers. The total score ranges from 0 to 60 with higher scores being indicative of the presence of depressive symptomatology.

Statistical analysis

In the present study, were used the software IBM SPSS statistics version 20 for analysis. The normal assumptions, after screening of data for violations of assumptions, revealed that wasn't violated for all variables. Chi-squared test and independent t-test were used for group-comparisons on demographics. Cronbach's a was used to evaluate the internal consistency in HC, ALS patients and their carers. Construct validity was assessed using Pearson's r between DAS total score and DAS dimensions and FBI and ECAS-Behavioral scale. For the comparison of groups (patients vs controls/carers) and subscales of DAS were used a mixed design analysis of factors (ANOVA-repeated measures) and post hoc

comparisons between groups (t-test). To examine the prognostic role of DAS dimensions on carers' burden, we used a linear regression model with ZBI as a dependent variable and the following predictors variables: ALS disease duration, ALSFRS-R, ECAS-ALS specific score, ECAS-ALS non-specific score, ECAS-Behavioral score, pDAS-Emotional, pDAS-Executive, pDAS-Initiation, iDAS-Emotional, iDAS-Executive, iDAS-Initiation. The statistical threshold was set at $p < 0.05$ for all analyses.

Results

Demographic characteristics of healthy controls and their DAS performance

Demographic characteristics and scores on administered inventories for the group of 100 HC are presented in Table 1. DAS scores were not associated with age and education and we did not find any gender difference ($p > 0.05$, ns).

Table 1. Demographic characteristics and scores on administered inventories for HC

Variables	HC (n=100)
Age (yrs)	55.35 (13.27)
Education (yrs)	11.52 (3.89)
Gender (M / F)	49 / 51
Depression (ADI)	17.88 (3.88)
DAS total	18.84 (9.20)
DAS executive	5.67 (4.20)
DAS emotional	5.16 (3.80)
DAS initiation	8.01 (3.59)

Note. HC = healthy controls; yrs = years; M / F = male / female.

Psychometric properties of DAS

Internal consistency. With regards to DAS internal consistency in the total sample of 100 HC, statistical analysis revealed high internal consistency (Cronbach's a = 0.87). The Cronbach's a value for total DAS was 0.87 for the ALS-version and 0.93 for carer-version.

Construct validity. DAS construct validity was evaluated within ALS patients and their carers. Table 2 presents significant correlations between DAS total score and DAS dimensions and scores on FBI and ECAS-Behavioral scale. We found significant correlations

between iDAS-total, iDAS-emotional and iDAS-initiation and FBI-total, FBI-negative and ECAS-Behavioral scores, as well as between pDAS-total and FBI-negative score. In all cases, higher DAS scores were associated with higher scores in FBI and ECAS-Behavioral scale.

Table 3. Correlations between apathy and other behavioral tests in ALS patients and their carers

	FBI-total	FBI-negative	ECAS-behavioral
iDAS-executive	-	-	-
iDAS-emotional	0.69**	0.72**	0.72**
iDAS-initiation	0.88***	0.87***	0.90***
iDAS-total	0.74**	0.77**	0.84***
pDAS-executive	-	-	-
pDAS-emotional	-	-	-
pDAS-initiation	-	-	-
pDAS-total	-	0.53*	-

*P<0.05, **P<0.01, ***P<0.001

Clinical utility of DAS: detecting apathy in ALS

From the total sample of 100 HC, we included 32 HC (15 males) with similar demographic characteristics with ALS patients (10 males). Both groups did not differ in age (ALS = 62.31 ± 10.7 yrs; HC = 59.91 ± 7.5 yrs; p = 0.656), education (ALS = 10.31 ± 3.8 yrs; HC = 10.34 ± 3.4 yrs; p = 0.932) or gender distribution (p = 0.152).

Patient-rated and HC comparison on the DAS

We found a significant main effect of diagnosis for patients and HC [F = 23.67; p < 0.001], with ALS patients being more apathetic in all dimensions. Furthermore, there was a significant main effect of dimensions [F = 16.031; p < 0.001] and significant interaction [F = 4.628; p = 0.012]. Further post hoc t-test analysis showed that within ALS there was significant difference between DAS-Emotional and DAS-initiation [t = -2.436; p = 0.031], while within HC, there was significant difference between DAS-Executive and DAS-Initiation [t = -8.438; p < 0.001], as well as between DAS-Emotional and DAS-Initiation [t = -4.998; p < 0.001). Patient-rated and HC scores in DAS dimensions are presented in Figure 1.

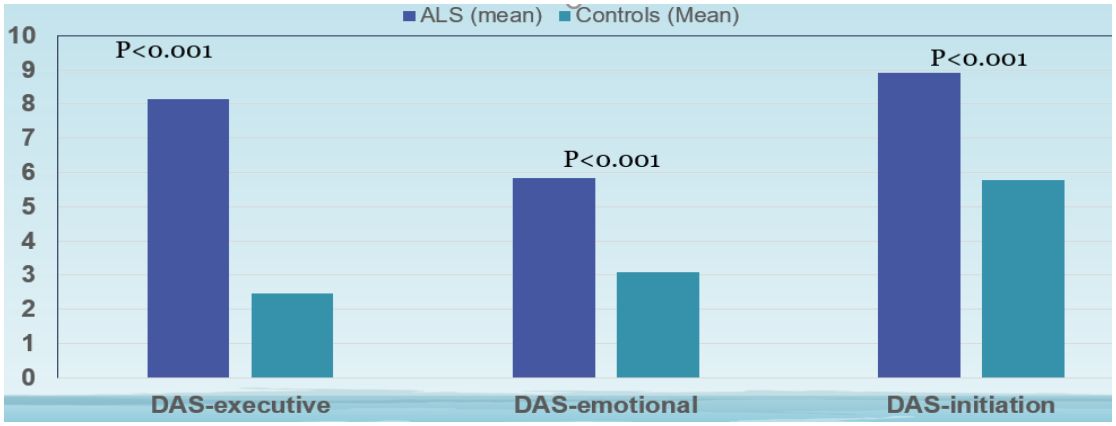

Figure 1.

Patient-rated and carer-rated comparison on the DAS

There was no significant main effect of diagnosis for patients and carers [F = 2.037; p >0.05]. There was a significant main effect of dimensions [F = 6.686; p = 0.003]. The interaction between diagnosis and dimensions was not significant [F = 0.458; p >0.05]. Post hoc analysis showed that in carers the DAS executive subscale and DAS emotional subscale differed significantly [t = 2.504; p = 0.028]. A similar pattern of differences (DAS executive vs. DAS emotional) was found in ALS [t = 1,799, p<0.05]. Patient-rated and carer-rated scores in DAS dimensions are presented in Figure 2.

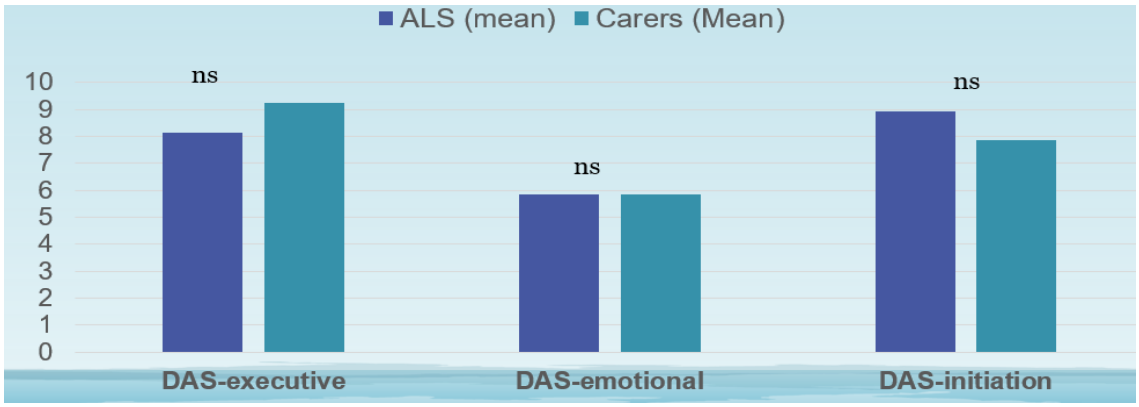

Figure 2.

Clinical utility of DAS: identifying prognostic role in carers' burden

According to the ZBI, 70% of carers reported high levels of burden (ZBI = 24.08 ± 17.77; cut-off score: 24). Regression analysis with the forward selection method (adjusted R2 = 0.688; F =20.85; p = 0.002) revealed that iDAS-Emotional was the only significant predictor for carers' ZBI score (b = 0.85; p < 0.002).

Discussion

Our study showed good psychometric properties (internal consistency and construct validity) of the DAS in Greek population.

1. Patients with ALS and HC showed significant differences in all DAS dimensions, with initiation being the most affected following by emotional and executive in HC and executive and emotional in ALS.
2. Considering patient-rated and carer-rated comparisons, we did not find significant differences on DAS dimensions.
3. We finally revealed that patients' emotional apathy as rated by their carers is a significant prognostic factor for carers' psychological burden even after controlling for ALS clinical characteristics (duration, functional disability), cognitive status and depression.

Previous research into apathy in ALS mostly considered and used scales which identified and assessed apathy as part of behavioral disturbances and as a unidimensional symptom with a lack of detailed analysis (Andrews et al., 2016, Caga et al., 2016, Lillo et al., 2012). Also, they used scales that were not specifically designed to assess patients with motor disability (Burke et al., 2015, Chio et al., 2010). However, in this study, we used the DAS which has been designed for patients with motor dysfunctions and we specifically evaluated the three dimensions of apathy (i.e. emotional; executive; initiation) in Greek speaking population and non-demented patients with ALS. The DAS showed good psychometric properties with high internal consistency in a healthy sample, as well as in a smaller sample of ALS patients and their carers. Furthermore, the associations between other general behavioral scales (i.e. FBI; ECAS-Behavioral) provides further evidence for its construct validity.

We found that 77% of our non-demented patients showed high levels of apathy, which is in line with previews studies reporting apathy as the most prominent behavioral symptom in ALS which affects 30-60% of patients (Caga et al., 2016, Chio et al., 2010, Radakovic et al., 2015, Santangelo et al., 2017). The DAS has been designed to evaluate different subtypes of apathy and was also a reliable tool for evaluation in other neurodegenerative diseases with or without prominent motor dysfunctions, including patients with Parkinson's disease and Alzheimer's disease (Radakovic et al., 2017). The evaluation of apathy with DAS has been validated in Parkinson's disease (Radakovic et al., 2017a) and in Alzheimer disease and is also associated with increased carers' distress in both (Radakovic et al., 2017b). The involvement of apathy in neurogenerative diseases might be associated with atrophy in both

dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) (Tsujimoto et al., 2011) and specific neuroanatomical changes might be presented as different dimensions of apathy (Levy et al., 2006, Levy, 2012). It will be interesting to use the DAS also in psychiatric disorders with the same neuroanatomical basis of apathy.

In the current study, comparing ALS with a subsample of healthy participants, we observed that all the DAS subscales of apathy were significantly affected. Another finding was the increased yield in initiation apathy compared to emotional and executive apathy both in patients and healthy participants, but still patients with ALS showed significantly increased initiation apathy. These seem to be in agreement with other studies (Radakovic et al., 2015). Initiation apathy associated with auto-activation deficit (i.e 'psychic akinesia' or 'athymormia') and implies pathology of the basal ganglia, globus pallidus and medial prefrontal cortex which were affected also in patients with ALS as well as Parkinson disease (Levy et al., 2006). On the other hand, increased emotional apathy seems to be associated with emotional processing, expression and recognition dysfunction (Goldstein et al., 2013). These processes had the same neurobiological background with social cognition and theory of mind (Girardi et al., 2011) which are also known to be affected in this population (Bora et al., 2016; Christidi et al., 2018). Furthermore, increased executive apathy seems to be related to attention, planning and organization difficulties and these processes are also associated with executive functions which are also affected in ALS (Pettit et al., 2013).

Also, in the current study we did not find differences between patients and carers rating in DAS. This is agreement with previews studies (Radakovic et al., 2015) and can be interpreted by the fact that we included non-demented patients who had mental potential and self-awareness and could assess and recognize these symptoms as well as it was done by their carers.

Previous studies in ALS have pointed out the impact of behavioral disturbances (Burke et al., 2015, Lillo et al., 2012, Chio et al., 2010) and disease factors (Gauthier et al., 2007, Goldstein et al., 1998) on carers' burden, which is quite high (Brulleti et al., 2014, Burke et al., 2015, Lillo et al., 2012, Qutub et al., 2014), as also revealed in our study (70% of our carers showed increased burden). The present study showed that when disease factors, patients' specific and non-specific cognitive impairment and general behavioral changes, as well as patient-rated and carer-rated apathy dimensions are all considered, the measures of cognitive functions and general behavioral changes and disease factors did not predict carers' burden. In contrast, it is patient emotional apathy as rated by the carer that predicts carers' burden. The absence of prognostic role of cognitive and disease related factors contrasts with

previous research of carers' burden in demented patients whose disease progression might not be as fatal as in ALS (Miller et al., 2013). There is no doubt that carers' burden can be also associated with depression. Indeed, secondary analysis in our sample (results not shown) revealed that carers' depression is highly associated with their ZBI score; yet supplementary regression analysis (results not shown) with carers' depression as dependent variable and patients disease and cognitive characteristics, as well as pDAS and iDAS scores as predictive variables, highlighted again the single predictive role of patient's emotional apathy as rated by the carer. This finding is highly important as it is related to the fact that the carers are more interested on emotional communication of their patients (Cacioppo et al., 2014, Galvin et al., 2016). Consequently, apathy is an important predictor factor that may cause high burden, lower quality of life and higher depression in ALS carers, which fits well with other studies (e.g. Chio et al., 2010) and highlights the importance of this emotional aspect rather than the common ALS motor disability (Lillo et al., 2012). It would be interesting to more thoroughly investigate the predictive role of distinct apathy dimensions in carers' burden in other neurodegenerative diseases.

Limitations

It is important to note that there were limitations in our study. First of all, the sample size of our patients and their carers was small and further larger studies are warranted. Also, pertinent to the Greek ethics and family issues towards disease, many patients might not be fully aware of the diagnosis and the progress of the disease which is often required by their carers. This was inevitable and may induce a bias in our study. Thus, direct comparisons between different populations are definitely needed in the future considering this factor as well.

Conclusion

Our study showed that the Greek version of DAS is a reliable and valid scale for measuring apathy and its subtypes in ALS. From a clinical point of view, not only we identified apathy in 70% of non-demented ALS patients but also observed that patients' emotional apathy as rated by their carers is the single most significant prognostic factor for carers' burden. Based on the latter and considering that apathy is a major risk factor for morbidity and mortality in ALS (Cacioppo et al., 2014), future multidisciplinary interventions are necessary in order to educate both patients and their carers. Such intervention should also focus on the characteristics that affect the burden of carers in order to reduce it (Andrew,

Pavlis, Staios & Fisher, 2016). This seems to have a positive effect on the patient; as patients realize that they are a burden for their relatives, they feel worse which is related to poor prognosis (Foley et al., 2016). Thus, by recognizing the spectrum of motor and extra-motor symptoms in ALS and specifically shedding light to apathy and its dimensions, a targeted support can be designed and provided to patients and their carers.

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