Journal of
Alzheimer's Disease & Parkinsonism

Riccitelli. J Alzheimers Dis Parkinsonism 2020, 11:1

Research Article Open Access

Different Awareness Domains Contributes to Explain Emotional and Behavioral Disorders in Mild Alzheimer's Disease

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Abstract

Background: The relationship between awareness domains and behavioural-psychological symptoms in Alzheimer's disease (AD) is unclear.

Objective: To investigate the effects of awareness domains on mild AD patients' emotional-behavioural disturbances and caregivers' stress accounting for demographic and clinical variables.

Methods: Overall awareness and cognitive, emotional and functional domains were investigated in 60 mild AD patients and 60 related caregivers using the Questionnaire of identification of deficits. The patients' cognitive functioning and psycho-affective/psychiatric symptoms, and their caregivers' stress, were also assessed. Patients were classified as preserved (AD_AP) and impaired (AD_AI) awareness. Hierarchical linear models were applied to explore the effects of awareness domains on psychological and behavioural measures.

Results: Unawareness was more frequent for emotional and functional disturbances than for cognitive deficits. AD_AP patients were less engaged in social and leisure activities and had higher rates of psycho-affective disturbances, while AD_AI had higher rates of psychiatric and behavioural disorders. Higher global awareness and higher awareness of cognitive alterations respectively explained 32% and 25 % of the variance for depression (both p: <0.001), higher awareness of emotional disturbances explained 23% of the variance for anxiety (p=0.022). Impaired awareness explained 33% of the variance for apathy symptom (p<0.001). Unawareness was also associated with higher caregivers' stress.

Conclusions: In mild AD patients, frequency of unawareness is domain-dependent. The relationship between awareness domains and emotional-behavioural disturbances is independent of demographic and clinical factors.

Keywords: Mild Alzheimer's disease; Awareness; Cognitive; Psycho-affective; Behavioural symptoms

Introduction

Awareness can be defined as the capability of an individual to accurately evaluate and report about his/her abilities and limitations [1]. It encompasses three dimensions: The ability to recognize a specific deficit, the emotional response to the difficulties and the ability to understand the impact of the impairment on functional activities [2-4].

Mild to severe unawareness is variably reported in dementia [2]. In cross-sectional studies of patients with Alzheimer's Disease (AD), awareness has appeared to decrease with increasing dementia severity, being negligible in mild-disease stages but substantially compromised in advanced disease [5].

Nevertheless, despite an increase in cognitive impairment severity and overall symptoms of dementia, longitudinal studies seem to partially contradict these findings, suggesting that deficits in awareness and cognition may be relatively independent [6,7]. Actually, unawareness in mild AD is mainly evident in poor recognition of changes in functional activities [6].

According to the literature, unawareness of deficits has been related to older age, worse cognitive functioning and neuropsychiatric disturbances, such as increased apathy, agitation, irritability, and psychosis [8-14].

Conversely, preserved awareness of dysfunction has been reported to be associated with psycho-affective symptoms, although this relation remains unclear [10,14,15]. Discrepant results across studies are evident in this respect, with some investigators reporting a positive association of awareness with depressive symptoms, others failing to find this relationship, and others observing a positive association of awareness with mild depression or dysthymia, but not with major depression [13,16-22].

In addition, awareness has been recognized as a multidimensional construct and the assessment of deficit in one of its particular domain does not always imply a reduction of awareness in the others [2, 23].

Consequently, each awareness domain could be affected by different factors [23,24]. About this, Lacerda and coworkers demonstrated a relationship between spared emotional awareness domain and depressive symptoms, impaired awareness of socio-emotional functioning and neuropsychiatric symptoms, and unawareness of cognitive functioning and caregivers' burden [23,24]. Despite these studies introduced a multidimensional construct of awareness, they overlooked the impact of potentially confounding factors on outcome-related variables in relation to awareness.

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Received December 03, 2020; **Accepted** December 23, 2020; **Published** December 30, 2020

Citation: Riccitelli GC, Defanti CA, Parietti N, Rossi S, Tiraboschi P, et al. (2020) Different Awareness Domains Contributes to Explain Emotional and Behavioral Disorders in Mild Alzheimer's Disease. J Alzheimers Dis Parkinsonism 10: 507.

It is arguable that taking into account the impact of demographic and clinical characteristics in the investigation of awareness changes might contribute to improve the understanding of the relationship between awareness domains and behavioural/psychological symptoms in AD patients.

In this study, after an assessment of unawareness domains' distribution, we applied demographic- and clinical- adjusted regression models to investigate the impact of awareness of cognitive, emotional, and functional disturbances on psycho-affective, behavioral and neuropsychiatric symptoms in mild AD patients.

The study findings could contribute to add new evidence useful to improve the management of patients with dementia.

Materials and Methods

Study participants

A consecutive series of 60 AD patients along with their primary caregivers was recruited from the outpatient AD clinic population of Alzheimer Center of Gazzaniga, Bergamo, Italy. All recruited AD patients have been diagnosed with probable mild AD defined by the criteria from the National Institute on Aging-Alzheimer's Association (NIA-AA) and presented with a Mini Mental State Examination (MMSE) score ≥ 20/30 [25,26]. The primary family caregiver was identified as that one mainly responsible for the AD patient, caring for him/her at least twice a week. All participants had no history of brain injury, stroke or any other neurological or psychiatric illness.

Local ethical committee approval and written informed consent from each individual were obtained before study initiation.

Measurements

Demographic and leisure activities investigation: An interview was performed by a neuropsychologist to investigate the patient's demographic and clinical characteristics, and a questionnaire was administered to quantify participation in physical and social leisure activities (LAs) during their early 20s, between 20 yrs of age and AD development and during the last year [27,28]. Total scores for the two kinds of activity performed in these periods were obtained summing the answers at each questionnaire item.

Functional assessment: The routine activity with or without needing assistance was investigated with the Activity Daily Living (ADL) scale, while the subject's ability to perform instrumental activities was assessed with the Instrumental Activities of Daily Living (IADL) scale [29].

Awareness assessment: The degree of awareness was investigated with the modified version of the Questionnaire of identification of deficits (QID) [30]. For each of the 26 items of the questionnaire, the patients were asked to rate how frequently they experienced any problems (not at all, some of the time, most of the time). The caregivers were also asked to rate the person with AD on the same items. Higher scores indicated fewer deficits. The items covered five domains (memory, instrumental activities, language, executive function and emotion). For the purpose of the study, the following have been considered: (i) an overall QID, (ii) a QID restricted to cognitive domains (QIDcog), which deals with the patient's awareness of memory, language and/or executive function, (iii) a QID restricted to emotion domain (QIDem), whose focus is the patient's awareness of his/her own emotional states and, finally, (iv), a QID instrumental activity domain (QIDfun), which only includes the items related to awareness of functional deficits in daily living.

Higher QID scores indicate lower awareness identification. For each dyad, both the patient's (QIDp) and his/her caregiver's (QIDc) scores were calculated and compared. For overall QID and each domain (QIDcog, QIDem, and QIDfunc) an Agreement Index (AI) was then calculated using the following formula:

$$AI = (QIDc-QIDp)/(QIDc+QIDp)*100$$

Where, AI ranges from -100 to +100, with 0 indicating the highest agreement between the patient and his/her caregiver, positive indices reflecting the identification of impairment by the caregiver, but not by the patient (indicating an underestimation of symptoms by the patient) and negative indices reflecting the identification of impairment by the patient, but not by the caregiver (indicating an overestimation of symptoms by the patient). The four indices obtained were used to describe QID domains, correlations and hierarchical regression models (overall QID: AI_QID, QIDcog: AI_QIDcog, QIDem: AI_QIDem, QIDfun: AI_QIDfun). Patients with an AI greater than +30 or lower than -30 were considered unaware of their deficits [30]. Moreover, to investigate emotional and behavioral characteristics in patients with global awareness impaired, AD patients unaware at three QID domains were classified as impaired (AD_AI).

Cognitive status assessment: A battery of validated tests was used to gather information on multiple domains related to cognitive functioning. Global cognitive abilities were assessed with MMSE, while selective cognitive abilities were assessed by tests devoted, respectively, to episodic memory (Short Tale), language (Token Test), phonemic and semantic fluency tests, speediness and executive functions (Trail Making Test (TMT)), attentional matrices, and frontal assessment battery (FAB) [26,31-36].

All patients were fully testable with the provided battery, and did not exhibit comprehension difficulty that could interfere with the execution of cognitive performances and the administration of questionnaire and scales. For each patient, test scores were corrected by gender, age, and education as appropriate. Then, the results on all tests were scored using a standardized method based on a comparison with the percentile distribution of values from normal controls [35]. The individual test scores ranged from 0 to 4, where every grade >0 means a normal performance. Individual test scores were summed up to provide a global composite cognitive score (CCS) for each patient [37]. Using function-related test scores, a composite cognitive score for memory (CCS_ME) and executive functions (CCS_EF) were also calculated. Lower CCS scores indicate poorer cognitive performances.

Emotional and behavior assessment: Depressive symptoms were evaluated with the Geriatric Depression Scale (GDS) with the supervision of a qualified interviewer who was unaware of the study purpose [38]. This scale has been tested and used extensively with the older population. It consists of a 30-item questionnaire to which participants are asked to respond by answering yes or no with regard to how they have been feeling over the past week. Higher GDS score indicates greater depression symptom.

Neurobehavioral symptoms were investigated with the Neuropsychiatric Inventory (NPI), a structured interview administered to caregivers to evaluate emotional and behavior alterations of AD patients [39]. Twelve behavioral domains are evaluated by the NPI: Delusion, hallucination, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time behavioral disturbances and changes in appetite/eating behavior. Each item is rated in relation to its frequency and intensity. Total score can range from zero to 144 points, and each domain score can range from 0 to 12 points; a higher score means a higher frequency/severity of neurobehavioral symptoms.

Caregiver's burden measurement: Caregiver Burden Inventory (CBI) was administered to evaluate the burden on different aspects of caregiver's life, which may be differentially affected by the relative's dementia [40]. Total score of CBI range from 0 to 100, with higher scores indicating a higher level of burden [41].

Statistical analysis

Normal distribution assumption was checked with Kolmogorov–Smirnov and Shapiro-Wilk tests, as well as with graphical inspection of Q-Q plots. Since the distribution of many of the outcome measures was skewed, non-parametric statistics that offered satisfactory alternatives to their parametric equivalents, without any significant loss of statistical power, were used. Parametric variables were described by their mean and Standard Deviation (SD), non-parametric variables by their median and Interquartile Ranges (IQR), and categorical variables by their frequency. Comparisons between AD preserved awareness (AD_AP) and AD_AI patients for demographic, clinical, LAs and ADL and IADL scores, as well as cognitive, GDS, NPI, CBI, were performed using the Pearson's chi-square test for categorical variables and Mann–Whitney U test for continuous variables. Correlation analyses were conducted between demographic, clinical, CCIs, neuropsychiatric variables, and AI_QID indexes. Partial correlations, adjusted for age, sex, and education, were also used to assess associations between overall AI_QID and AI_QID domains (AI_QIDcog, AI_QIDem, AI_QUIDfunc) scores and all variables investigated (demographic, clinical, functional, cognitive, emotional and behavioral, as well as caregiver's burden measures). Then, a hierarchical regression model was applied to evaluate the role of awareness in explaining portions of depressive symptoms and neurobehavioral disturbances variance unrelated to demographic, daily-life activities, clinical and cognitive measures. Model included: Age, sex, education, and disease duration (block 1), LAs, functional activities (ADL, IADL), and cognition (CCS) (block 2), the overall and AI_QID domains (block 3), in a within-block stepwise approach.

Collinearity for all variables was assessed considering a tolerance >0.1 (or VIF<10).

All statistical analysis was performed with SPSS software for Windows version 23.0 and R software 3.3.0.

Results

Table 1 summarizes the main demographic and clinical features of mild AD patients enrolled (Table 1). The study group included 20 men and 40 women patients with a mean age of 79 years ± 5.8 and a mean education of 5.7 years ± 2.4. In addition, mild AD patients had a mean MMSE of 22.3 ± 2.4 and a mean disease duration=28.4 ± 23.1 months. As expected, they showed mild dependence in activities of daily living (median ADL=5 [IQR=3-6]) and moderate dependence for the instrumental daily activities (median IADL=3 [IQR=2-5]. Compared with the years before the diagnosis, AD patients showed reduced frequency of physical and, especially, social LAs (median social LAs variation after- before AD= -3.0 [IQR=-6.0-1.0], median physical LAs variation after-before AD= -1.0 [IQR=-2.0-0.0]).

Awareness findings

Thirty-nine AD patients were unaware of their global disturbances (overall AI_QID: 65%), 32 patients showed impaired awareness for cognitive dysfunctions (AI_QIDcog: 53.3%), 44 patients showed unawareness for functional limitations (AI_QIDfun: 73.3%) and 48 patients showed unawareness for emotional disturbances (AI_QIDem: 80%). The frequency of unawareness of functional dysfunction was greater than that related to cognitive deficits (AI_QIDfun vs AI_QIDcog: p=0.010), while no significant differences emerge from the comparison of other domains (AI_QIDcog vs AI_QIDem: p=0.050, AI_QIDfun vs AI_QIDem: p=0.716).

Of the 60 AD patients, 25 (41.6%) were impaired on all three awareness domains, 18 (30%) were impaired on two domains, 13 (21.6%) were impaired on just one domain, and the remaining four were not impaired at all on any AI_QID index (6.7%).

To better define the demographic, clinical and neuropsychiatric characteristics of the patients' awareness impairment, independently by domains, patients with awareness impaired on all AI_QID indexes were classified as AD_AI patients (N=25), while the remaining were considered AD_AP (N=35). Table 2 summarizes the median of AI_QID indices, observed in all AD sample and AD_AP and AD_AI subgroups (Table 2).

Comparison between AD with impaired and preserved awareness

AD_AP and AD_AI patients were matched for all demographic measures, and comparable for clinical variables, including the degree of autonomy in daily life and cognitive impairment.

From the comparison between groups, AD_AP patients reported lower participation at social leisure activities (e.g. visiting friends, attending organized social or group activities, and participating in structured group activities) after the AD diagnosis (p=0.44) and higher GDS scores than the AD_AI patients (p<0.001). See Table 3 for further details.

Interesting results about neurobehavioral findings, although not reaching the significance level, were found in the AD_AP patients, who exhibited a higher total NPI score indicative of major neurobehavioral disturbances (0.081). A more defined profile appeared in the NPI sub domain scores, from which it emerged that AD_AP patients had greater agitation (p=0.041), dysphoria/depression (p=0.001), anxiety (p=0.028), and irritability (p=0.031) compared with their AD_AI counterparts.

Table 1: Main demographic and clinical characteristics of mild AD patients.

Variables	AD Patients (N=60)
Sex (M/F)	20/40
Median Age (IQR)	80 (75-84)
Median Education [years] (IQR)	5 (5-6)
Median Disease Duration [months] (IQR)	22 (13-34)
Median MMSE score (IQR)	22 (20-24)
Median IADL (IQR)	3 (2-5)
Median ADL (IQR)	5 (3-6)

Abbreviations: AD: Alzheimer's disease; M: Man; F: Female; IQR: Interquartile Range; MMSE: Mini-Mental State Examination; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living

Table 2: Median and interquartile range of AI_QID measures in all mild AD patients and mild AD patients with preserved and impaired awareness.

Awareness measures	AD patients	AD_AP patients	AD_AI patients
	N=60	N=35	N=25
Median AI_QID global score (IQR)	36.36 (18.2-51.4)	25.00 (6.3-36.1)	55.00 (47.1-64.8)
Median AI_QIDcog score (IQR)	30.77 (12.5-46.3)	17.20 (7.3-25.8)	60.10 (48.2-56.5)
Median AI_QIDem score (IQR)	33.33 (9.5-100)	20.00 (0.0-60)	60.00 (33.3-100)
Median AI_QIDfunc score (IQR)	50.00 (20.0-100)	33.33 (11.8-61.9)	63.61 (42.9-100)

Abbreviations: AI_QID: Agreement index of Questionnaire of identification of deficits; AD: Alzheimer's disease; AD_AP patients: AD with preserved awareness, AD_AI patients: AD: Patients with impaired awareness; AI_QIDcog: AI_QID of cognitive domain; AI_QIDem: QID of emotional domain; AI_QIDfunc: QID of functional domain; IQR: interquartile range.

Table 3: Comparisons between AD_AP and AD_AI patients for demographics, clinical, cognition, and emotional variables.

Variables	AD_AP patients	AD_AI patients	p
	N=35	N=25	
Sex (M/F)	11/24	9/16	1.0
Median Age (IQR)	80.0 (72.5-82)	80.5 (75-84)	0.534
Median Age onset (IQR)	77.0 (72-80)	77.5 (72-82)	0.804
Median Education years (IQR)	5.0 (4.0-5.0)	5.0 (4.0-8.0)	0.546
Median DD months (IQR)	17.0 (11.0-31.5)	24.0 (13.0-36.0)	0.096
Median IADL score (IQR)	3.0 (2.5-5.5)	3.0 (2.0-5.0)	0.753
Median ADL score (IQR)	6.0 (3.0-6.0)	6.0 (3.0-6.0)	0.514
Median physical LAs change (IQR)	-2.0 (-2.0 - 0.0)	-1.0 (-2 - 0.0)	0.351
Median Social LAs change (IQR)	-3.0 (-6.0 -1.0)	-2.0 (-5.5- 0.25)	**0.044**
Median CCS (IQR)	6.0 (2.0-12.0)	6.0 (3.0-11.0)	0.976
Median CCS_ME (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.251
Median CCS_EF (IQR)	3.0 (1.0-7.0)	3.0 (1.0-6.0)	0.970
Median GDS (IQR)	13.0 (9.0-16.0)	9.0 (8.0-11.0)	**<0.001**

Abbreviations: AD_AP patients: AD with preserved awareness; AD_AI patients: AD: Patients with impaired awareness; M=Man; F=Female; IQR: interquartile range; DD: Disease duration; IADL: Instrumental activities of daily living; ADL: Activities of daily living; LA: Leisure activity; CCS: Global composite cognitive score; CCS_ME: Memory composite cognitive score; CCS_EF: Executive function composite cognitive score; GDS: Geriatric depression scale. P values showing significant differences between the two AD patients groups are in bold

On the other hand, compared with AD_AP, AD_AI patients had higher delusions (p=0.038), apathy (p=0.002), aberrant motor behaviour (p=0.018) and eating disorders (p=0.034) scores (Table 4).

Finally, greater assistance burden was reported by the caregivers of the AD_AI patients (p=0.033).

Correlation findings in AD patients

Significant correlations were found between:

- Higher level of awareness (overall AI_QID) and lower social LAs after AD diagnosis (r=0.349, p=0.007), higher self-report depression (GDS, r= -0.568, p<0.001), higher proxy report dysphoria/depression (NPI_dysphoria, r= -0.554, p<0.001), and higher anxiety (NPI_anxiety, r= -0.297, p<0.021); while lower awareness was correlated with greater apathy (NPI_apathy, r=0.498, p<0.001).
- Higher awareness of cognitive dysfunction correlated with lower social LAs after AD diagnosis (r=0.355, p=0.006), higher depression (GDS: r=-0.559, p<0.001) and higher dysphoria (NPI_dysphoria/depression: r=-0.514, p<0.001), while lower awareness of cognitive dysfunction correlated with apathy scores (NPI_apathy: r =0.367, p=0.004).
- Higher awareness of emotional disturbances (AI_QIDem) was associated with lower social LAs after AD diagnosis (r=0.273, p=0.041) and higher anxiety (NPI-anxiety: r=-0.383, p=0.004). Reduced awareness at AI_QIDem correlated with apathy (NPI_apathy: r=0.247, p=0.050).
- Higher awareness of reduced functional activity (AI_QIDfun) correlated with higher self- report depression score (GDS: r=-0.386, p=0.003) and higher proxy-report dysphoria (NPI_dysphoria: r=-0.398, p=0.002). Reduced awareness on AI_QIDfun was associated with higher proxy-reported apathy (NPI_apathy: r=0.308, p=0.020).
- Higher level of Caregiver's burden correlated with all lower AI_QID, except for AI_QIDem (AI_QID: r=0.790, p<0.001; AI_QIDcog: r=0.809, p<0.001, AI_QIDem: r=0.313, p=0.018).

No significant correlations were found between QID indexes and all composite cognitive scores (CCS, CCS_ME, CCS_EF).

Effect of awareness domains level on emotional and behavioural disturbances

The hierarchical regressions in which each AI_QID score was included separately at block 3 showed:

- Negative effect of AI_QIDcog (indicator of awareness of cognitive limitations) for self-reported depression symptoms (GDS: β= -0.559, R^2 =0.326, p<0.001),
- Negative effect of overall AI_QID (indicator of global awareness of cognitive, emotion, and functional limitations) for depression/dysphoria symptoms as assessed by caregivers (NPI_dysphoria: β=-0.500, R^2 =0.250, p<0.001),
- Negative effect of AI_QIDem (indicator of awareness of emotional limitation) for proxy-reported anxiety (NPI_anxiety: β= -0.372, R^2 =0.227, p=0.022),
- Negative effect of global unawareness of oneself limitations (overall AI_QID) was found for proxy-reported apathy (NPI_apathy: β=0.530, R^2 =0.328, p<0.001).

Table 4: Median and interquartile range of neuropsychiatric inventory scores in AD patients,, classified according to preserved (_AP)/impaired (_AI) awareness.

Neurobehavioral variables	AD_AP	AD_AI	p
	patients N=35	patients N=25	
Median NPI Total score (IQR)	41 (28.5-55.5)	30 (23-45)	0.081
Median NPI Delusion (IQR)	0.0 (0.0-3.0)	2.0 (0.0-6.0)	***0.038***
Median NPI_Hallucination (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.704
Median NPI_Agitation (IQR)	4.0 (1.0-8.0)	2.0 (0.0-5)	**0.041**
Median NPI_ Depression/ Dysphoria (IQR)	7.0 (4.0-10)	3.0 (1.0-6.0)	**0.001**
Median NPI_Anxiety (IQR)	7.0 (4.0-12)	5.0 (3.0-8.0)	**0.028**
Median NPI_Euphoria (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.756
Median NPI_Apathy (IQR)	2.0 (0.0-4.0)	6.0 (2.0-9.0)	***0.002***
Median NPI_Disinibition (IQR)	0.0 (0.0-2.5)	2.0 (1.5-4.0)	0.274
Median NPI_Irritability (IQR)	6.0 (2.0-12.0)	4.0 (1.0-6.0)	**0.031**
Median NPI_Aberrant Motor Behavior (IQR)	0.0 (0.0-4.5)	4.0 (0.0-6.0)	***0.018***
Median NPI_Sleep disturbances (IQR)	1.0 (0.0-5.0)	0.0 (0.0-2.0)	0.186
Median NPI_Eating disorders (IQR)	0.0 (0.0-2.0)	2.0 (0.0-4.0)	***0.034***

Abbreviations: AD_AP patients: AD patients with preserved awareness, AD_AI patients: AD: Patients with impaired awareness; NPI: Neuropsychiatric Inventory; IQR: interquartile range. P values showing significant impaired in AD_AP patient group are in bold, while P values showing significant impaired in AI_AP patient group are in bold and italics

Discussion

Our study showed that the distribution of impairment in the different domains of awareness is not uniform, with a higher frequency of unawareness for emotional and functional disturbances than for cognitive impairment.

The relation of awareness to psycho-affective and behavioral disturbances depends on whether awareness is impaired or relatively spared. Specifically, mild AD patients with preserved awareness of their deficits had higher depression/dysphoria, agitation, anxiety, and irritability, whereas those with impaired awareness had greater apathy, delusion, aberrant motor behavior, and eating disorders.

Considering the different awareness domains, a more detailed profile has been delineated about the association of awareness with emotional and behavioral disturbances. Indeed, preserved awareness of global, as well as cognitive and functional disturbances was positively correlated with depression and anxiety symptoms, while decreased awareness for all domains investigated was associated with apathy alone. Finally, controlling for demographic and clinical variables, increased awareness of both global and cognitive deficits contributed to explain the presence of higher depression symptoms, whereas increased awareness of emotional disturbances explained higher level of anxiety. Conversely, global unawareness was related to greater apathy and also contributed to caregiver stress.

Unawareness of emotional and functional abnormalities appeared to be most frequent than unawareness of cognitive limitations in everyday life (80% vs 53.3% and 73.3%, respectively), confirming that impaired awareness is structured differently in relation to different domains.

Arguably, unawareness of the emotional and functional changes more than cognitive deficits could result from psychological defense mechanisms, such as the role of defensive denial, or personality factors in the first stages of dementia [42]. Moreover, the high frequency of both domains could confirm the hypothesis of the probable influence of functionality in other awareness domains [23]. Further studies, including a greater number of AD patients, could contribute to investigating this hypothesis.

In line with previously evidence, we did not find significant differences between mild AD patients with impaired and preserved awareness for cognitive functioning, supporting the hypothesis that low awareness is related to advanced disease stages rather than to single cognitive domains [17,43]. We can also speculate that in the early stages of AD, most patients have some awareness of their cognitive limitations and may try to apply strategies to compensate them or consult physicians; as the disease advances, the awareness decreases, so that patients may become indifferent to their condition. Conversely, several studies have indicated that a lower level of awareness was associated with greater global dementia severity [44-47].

These contradictory results confirm that awareness is heterogeneous and a non-linear phenomenon [48,49]. Nevertheless, we cannot exclude that awareness impairment could be a sensitive marker of dementia progression over time as well as awareness deficit in subjects with Mild Cognitive Impairment (MCI) might be a predictor of a more malignant course of the disease.

AD patients with intact awareness showed a reduced involvement in social leisure activities after the AD diagnosis. This finding was further confirmed by the correlation analysis, which showed a significant relationship between higher awareness of global, cognitive and emotional deficit and reduced participation in social leisure activities. This social retirement could be due to these patients' awareness of cognitive dysfunction acquired with the illness, such as word retrieval difficulty or memory decline. In line with this hypothesis, a previous study demonstrated that patients with MCI and mild AD were more distressed by self-detected problems in cognitive skills needed for social interaction than other cognitive domains [50].

In AD patients with preserved awareness we also found an association between social retirement and greater awareness of emotional dysfunctions, suggesting that the awareness of emotional/ behavioral modifications induces these patients to avoid social entertainment, with consequent isolation and lower quality of life in this phase of the disease. This hypothesis is strengthened by previous evidence that showed lower quality of life in AD patients with higher awareness of their deficits [4,15,23,51].

Mild AD patients with greater awareness of their deficits/ limitations reported higher depressive symptoms and their caregivers described them as also having a higher frequency of agitation, anxiety and irritability disorders in daily life. In addition, a relevant association was found between higher awareness of global, cognitive or functional

deficits and higher level of depression (either self-reported or reported by the caregiver). Depression, behavioral and psychological symptoms may be an emotional reaction resulting from the recognition of acquired disturbances, suggesting that the awareness of wrong attitudes could elicit a depressive reaction and higher levels of anxiety, agitation, and irritability [49].

Using hierarchical regression linear models, we found that, among the different awareness domains investigated, the awareness of cognitive deficits contributed more than other awareness domains to explain depressive symptoms in mild AD patients. Probably, the awareness that cognitive dysfunction could be one of the first and most disabling symptom of illness induces feelings of sadness and hopelessness in these patients. Starkstein et al. found that depression was related to higher levels of cognitive awareness, and subsequently the same authors suggested that dysthymia may occur in patients with higher levels of awareness as an emotional response to cognitive decline [22]. Other studies demonstrated a relationship between less severe forms of depression, like dysthymia, and greater awareness of a particular deficit, indicating that dysthymia may be an emotional reaction to the change associated with the disease [14].

Mood disturbances, such as feeling depressed, therefore, would be more likely to occur in patients who have awareness of inevitable decline than in those who are unable to understand or accurately appraise the gravity of their disease state.

In addition, the awareness of disease deficits appeared to have an effect on dysphoria manifestation, suggesting that a greater awareness of disturbances increases the psychiatric symptoms. This evidence is in line with previous studies indicates that dysthymia may be a psychosocial reaction to the changes associated with the disease [14,22].

Our findings showed also that greater awareness of emotional disturbances had an impact on anxiety level, suggesting that greater awareness of emotional changes may lead these patients at continuous alertness and agitation so as to try to control modify their behavior. Lacerda and coworkers showed that awareness of emotional domain functioning was related to gender, neuropsychiatric symptoms and ADL in AD patients [24]. Previously, several studies found a relationship between greater awareness and anxiety, and a significant relationship between insight and anxiety after controlling for cognitive functioning [9,12,52].

In line with previous studies, we found that mild AD patients with unawareness of their deficits showed delusion, apathy, aberrant motor ability and eating disorders [9,20,22,53,54].

However, it is worth highlighting that some studies showed an involvement of cognitive impairment in this association. Vogel and co-authors demonstrated that unawareness was related to a lower global cognitive functioning, hypothesizing that it may contribute to the occurrence of neuropsychiatric symptoms even in early phases of AD, whereas De Carolis and coworkers showed that anosognosia was related to psychiatric and behavioral disturbances, as well as to memory and executive deficits, according to the specific functional anatomy of the symptoms [10,55].

Albeit our results confirmed a relationship between impaired awareness and disturbances mainly of psychiatric nature, we did not find a significant association between awareness alterations and cognitive impairment of patients. This discrepancy might mainly be due to the application of different diagnostic methods and different severity of cognitive impairment of patients included in the studies. Nevertheless, we do not exclude that the impairment of awareness could be independent of cognitive functioning especially in the early stage of dementia, in which it is expected that the functioning of brain regions should be more preserved. Further studies in different stages of disease should contribute to clarify the relation between the two disturbances in AD.

According with previous studies we found a relationship between unawareness and apathy for all awareness domains investigated [9,10,56]. Then, unawareness of daily life disturbances explained about 28% of the variance of the apathy behavior in our AD patient's sample.

Vogel et al. hypothesized that the right inferior frontal gyrus might be a crucial area for impaired awareness [57]. Previous studies, using different advanced imaging techniques, showed a pattern of brain regions involved in the occurrence of unawareness in AD patients, mainly located in the frontal regions, cingulum and temporo-parietal regions [58-60].

On the other hand, apathy symptom appears to be related to abnormalities of frontal regions, anterior cingulate cortex, also including deep GM regions [61-64].

Taking together, these evidences and our results suggest that unawareness and apathy might share neurobiological underpinnings and their relationship might be independent of different awareness domains. Future studies, including advanced neuroimaging techniques and clinical tools to assess awareness and psychiatric disturbances, could contribute to explain whether unawareness and apathy are related to the same brain regions damage.

Our analysis also revealed a correlation between lower awareness for cognitive, functional and emotional deficits and higher caregiver's burden, suggesting that unawareness has important implications in the caregiver's perception of physical and mental burden. We found this impaired awareness of deficits correlated to aberrant motor behavior, eating disorders and delusion episodes: All conditions requiring greater patient's assistance.

Previous studies demonstrated that caregivers face difficulties in the management of AD patients with dangerous behaviors with consequent burden increase [8,47,65]. Specialized assistance programs or primary care focusing on the management of abnormal behavioral should be taken into account by physicians to reduce caregivers' stressful experiences.

The strength of the present study lies in the fact that it provides a description of the impairment occurrence of each awareness domain in mild AD patients, using analysis models that controlled for demographic, social and clinical factors potentially influencing the relationship between different awareness domains and behavioral psychological symptoms. Finally, an extensive neuropsychological evaluation allowed an accurate investigation of cognitive dysfunctions in the sample studied.

Nevertheless, the present study has some limitations. Firstly, the relatively small sample size, especially regarding the preserved and impaired awareness comparison, induces to consider results as exploratory. Secondly, our data are cross-sectional and longitudinal studies can better identify the extent of deficits and the patterns of change in awareness over time, as awareness is not a static phenomenon. Finally, our sample includes only mild AD patients: Future studies should compare results of patients with mild and more advanced states of AD and should include a control group of healthy subjects.

Conclusion

In conclusion, our study indicate that independently of demographic and clinical characteristics, subjects with early-stage of AD and higher level of awareness of cognitive and emotional alterations were affected by psycho-affective symptoms such as depression and anxiety, maybe as a result of a psychological reaction to noticing daily lives performances' decline.

On the other hand, unawareness of deficits, independently of related domains, appeared to explain a portion of apathy. Arguably, both awareness impairment and apathy are related to the same neuropathological substrates so their expression could be consequent to damage of selected brain regions and might be a predictor of disease progression over time. These hypotheses should be addressed using standardized instruments to investigate different domains of awareness and advanced neuroimaging techniques in future longitudinal studies.

Overall, this study supports the introduction of accurate evaluation of global awareness and its domains in the clinical assessment in mild AD patients. This approach could contribute to provide better intervention for care and management of patients with dementia as well as to improve the quality of life of the caregivers.

Declarations

Acknowledgments

Erica Chitó and Marta Sala performed neuropsychological and behavioral assessment at participants.

Conflict of interest/disclosure statement

The authors have no conflict of interest to report.

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