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Apathy Is the Best Dimension to Consider for Awareness Assessment in Alzheimer's Disease

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1 **Abstract**

2 Previous studies have reported the major role of apathy in awareness assessment among
3 Alzheimer's patients using the *patient-caregiver discrepancy* method, whatever the awareness
4 dimension assessed. Using the *Apathy Evaluation Scales* among other awareness scales, we
5 report that apathy is the sole awareness dimension distinguishing healthy controls (25), mild
6 (57) and moderate-to-moderately-severe (11) Alzheimer's patients. A linear regression
7 showed that the *Mini-Mental State Examination* score used as a risk factor for non-awareness
8 was the only factor associated with awareness of apathy and was the best predictor. This
9 suggests that apathy is the most discriminant dimension for awareness assessment in
10 Alzheimer's disease.

11 **Key-words:** Alzheimer's disease – Awareness – Apathy – Assessment method

1 **1 Introduction**

2 Lack of awareness of their own deficits is commonly observed among patients with
3 Alzheimer's disease (AD). This can increase with disease progression, complicating
4 management because patients refuse assistance, thinking they do not need it [1].

5 Awareness is usually assessed using three methods. The *patient-caregiver discrepancy*
6 method, using caregiver ratings as the reference, and subtracting patient ratings. The *clinical*
7 *rating* methods use structured patient interviews on different impairment domains. The
8 *prediction of performance discrepancy* method where scores on tests used are the reference to
9 be compared to predictions [1].

10 Lack of awareness has been found to be associated with executive functions and more
11 particularly with dysexecutive behavioural symptoms. Using a longitudinal methodology,
12 Starkstein et al [2] reported that patients with impaired awareness were more apathetic than
13 those with better awareness, and that apathy increased with the progression of the disease.
14 Horning et al. [3] reported a positive association between behavioural disturbances and lack
15 of awareness. This association was particularly pronounced for apathy and lack of awareness.
16 Starkstein et al. [4] found anosognosia to be the best predictor of apathy in AD. More
17 recently, in a review of literature, Azocar et al. reported that the majority of studies assessing
18 the relationship between impaired awareness and apathy in mild-to-moderate AD showed a
19 significant positive association [5]. In addition, apathy is the commonest symptom at any
20 stage in the disease [6-7]. Conversely, better awareness has been frequently found to be
21 associated with greater depression [5, 8].

22 Since associations between poorer awareness, lesser depression and greater apathy have been
23 reported, the role of assessment methods has been studied, showing associations with apathy
24 scored by a relative or a clinician, whatever the assessment method used, [9]. Indeed, the

1 *patient-caregiver discrepancy* method clearly shows the involvement of apathy scored by a
2 relative whatever the awareness dimensions explored [10], suggesting that lack of awareness
3 could be a main component of apathy. This does not contradict studies suggesting the
4 multidimensionality of awareness, because multidimensionality entails various components of
5 awareness such as different cognitive functions, behaviours and emotional expressions. All of
6 this can be modulated and even inhibited by apathy, which could explain why, with certain
7 statistical analyses, awareness appears multidimensional whereas modelling awareness using
8 regression analysis can reduce it to a few factors supervising the others.

9 Because apathy, meaning a lack of initiation and interest relating to various dimensions of
10 cognition, behaviour and emotions, is involved whatever the awareness dimension assessed
11 using the *patient-caregiver discrepancy* method, it could be the most discriminant awareness
12 dimension to be explored in AD using this method. Here, we predicted that apathy could be
13 the most discriminant awareness dimension over and above the cognitive, behavioural,
14 emotional, relational and daily living autonomy awareness dimensions among patients with
15 mild-to-moderately-severe AD, compared to healthy controls.

16 **2 Method**

17 2.1 Participants

18 The study included 93 participants. Twenty-five were Healthy Controls (HC) recruited from a
19 pool of previous participants. Sixty-eight participants were Alzheimer's patients, according to
20 the National Institute on Aging and the Alzheimer's Association Working Group diagnostic
21 guidelines for AD [11], recruited from a memory center. The disease stage was determined
22 using the *Mini Mental State Examination* (MMSE score) [12-13]. Fifty-seven (57) patients
23 presented mild Alzheimer's disease ($20 \leq \text{MMSE} < 30$) and 11 a moderate-to-moderately-severe
24 form ($10 \leq \text{MMSE} < 20$). In fact, only one patient with a moderately-severe form (MMSE=13)

1 was able to complete the scales and was therefore included in this group. Most patients had
2 already been recruited in our previous studies [9-10] and we added only 7 Alzheimer's
3 patients. All participants signed consent to participate and the study was approved by the local
4 ethics committee.

5 2.2 Evaluation tools

6 2.2.1 Cognitive assessment

7 All participants were assessed using the MMSE, and the *Frontal Assessment Battery* – FAB
8 [14]. In order to ensure the absence of anterograde memory impairment (possible Mild
9 Cognitive Impairment) among healthy controls, we systematically used the *Free and Cued*
10 *Recall Test* – FCRT [15] and the *Delayed Match to Sample* test – DMS-48 [16]. Healthy
11 controls perform normally for all cognitive tasks (MMSE, FCRT, DMS-48 and FAB).

12 2.2.2 Awareness assessment

13 All participants were assessed using three awareness scales related to the *patient-caregiver*
14 *discrepancy* method.

15 The Patient Competency Rating Scale – PCRS [17] including four sub-scales: "*Activities of*
16 *Daily living (ADL)*", "*Cognition*", "*Interpersonal Relations*" and "*Emotions*". This scale asks
17 the participant and a relative the same 30 questions on the participant's ability to perform
18 various daily-living activities. Levels of awareness on the overall scale and each sub-scale are
19 assessed by subtracting the participant's rating from the relative's rating. Higher scores
20 indicate greater awareness.

21 The *Anosognosia Questionnaire for Dementia* – A-QD [18] including "*Cognitive*" and
22 "*Behavioral disturbances*" sub-scales, designed on the same principle as the PCRS.
23 Awareness is scored in a similar manner to the PCRS, but lower scores indicate greater
24 awareness.

1 The *Apathy Evaluation Scale* – AES [19] asks the participant, a relative and the clinician the
2 same 18 questions on apathy levels presented by the participant in the two previous weeks.
3 For all versions of apathy measures, lower scores indicate greater apathy. Awareness of
4 apathy was obtained by subtracting the patient rating from the relative rating, and here higher
5 scores indicate greater awareness of apathy.

6 2.2.3 *Mood/behavioural assessments*

7 We used the *Geriatric Depression Scale* – GDS [20]. This scale is based on a self-evaluation,
8 where higher scores indicate greater depression. For apathy, we used the *Apathy Evaluation*
9 *Scale* – AES, based on a hetero-evaluation completed by the clinician (AES_{Clinician}) [19],
10 where lower scores indicate greater apathy.

11 2.3 Statistical analyses

12 The statistical analyses were performed using R software (version 4.1.1) (prettyR package).
13 Because some groups comprised < 30 , we used a non-parametric ANOVA with Holm
14 adjustments for multiple comparisons. On the overall sample including healthy controls, we
15 performed a linear regression using the stage of the disease, determined with the MMSE
16 score, as the risk factor for impaired awareness of apathy in order to identify the interactions
17 between the risk factor and awareness [9-10].

18 3 Results

19 Table 1 reports performances across healthy controls, mild and moderate-to-moderately-
20 severe Alzheimer's patients. Healthy controls were younger ($W=24.05$, $p<0.0001$) and more
21 educated than patients ($W=11.87$, $p=0.0026$) who did not differ across subgroups. The three
22 groups were comparable for gender ($p>0.05$). Healthy controls performed significantly better
23 than patients for all variables except for depression where all groups were comparable (GDS:
24 $p>0.05$). Only four variables distinguished the three groups (healthy controls $>$ mild

1 Alzheimer > moderate-to-moderately-severe Alzheimer). These were the MMSE (W=64.35,
2 $p<0.0001$), which is logical because it was used to distinguish the groups, the FAB (W=38.39,
3 $p<0.0001$) relating to executive functioning, apathy, only scored by a relative (AES_{Relative}:
4 W=37.05, $p<0.0001$) and awareness of apathy obtained by subtracting AES_{Patient} from
5 AES_{Relative} (W=18.39, $p=0.0001$).

6 Concerning awareness dimensions, only apathy distinguished the three groups (W=18.39,
7 $p=0.0001$). Concerning the PCRS, the total score, the Activities of Daily Living sub-scale and
8 the Cognition subscale distinguished healthy controls from patients without taking into
9 account the disease stage (healthy controls / patients, respectively: W=16.64, $p=0.0006$;
10 W=9.09, $p=0.0102$; W=20.56, $p<0.0001$). The PCRS Emotions sub-scale and the PCRS
11 Relations sub-scale only distinguished healthy controls from mild Alzheimer without
12 distinguishing moderate-to-moderately-severe Alzheimer from the previous two (respectively:
13 W=8.019, $p=0.0181$; W=7.892, $p=0.0193$). Finally, for the A-QD, the total score, and the
14 intellectual and behavioural subscale scores distinguished healthy controls from patients
15 without taking into account the disease stage (healthy controls / patients, respectively:
16 W=17.33, $p=0.0001$; W=17.03, $p=0.0002$; W=9.518, $p=0.0085$).

17 We also performed a manual backward regression for awareness of apathy (AES_{Relative} -
18 AES_{Patient}) using the disease stage (MMSE score) as a risk factor. In addition to the risk factor
19 maintained in the model, we entered the following variables: Age, Education, Gender, IADL,
20 FAB, GDS relating to depression and AES_{Clinician} for apathy. We maintained confounding
21 factors impacting at least 15% of the risk factor estimate in the model [9-10]. The only factor
22 associated with awareness of apathy was the risk factor itself ($\beta=1.17$, IC95%=0.64-1.69,
23 $p<0.0001$), without confounding factors. The model showed normal fit (W=0.99, $p=0.81$) but
24 homoscedasticity with the Snedecor test was debatable (F=0.21, $p<0.0001$).

1 Finally, because the risk factor was the only variable remaining in the model, the MMSE
2 score was the best predictor of awareness of apathy, explaining 17.62% of the variance.
3 Nevertheless, this not exclude other associations such as that between the AES_{Clinician} and the
4 MMSE ($r= 0.636$, $p<0.0001$), and awareness of apathy and the AES_{Clinician} ($r= 0.366$,
5 $p=0.0003$).

6 After adjusting our model on age and education, MMSE and age were significantly associated
7 with awareness of apathy (respectively $p=0.0028$, and $p=0.01847$), and the three factors
8 explained 20.57% of the variance against 17.62% for the MMSE alone. Although, the last
9 factor removed impacted 16.2% of the risk factor estimate, this could be acceptable given that
10 it should no exceeded 20% [9].

11 **4 Discussion**

12 Our hypothesis that awareness of apathy could be the most discriminant dimension for
13 awareness assessment using the patient-caregiver discrepancy method appears valid.

14 Firstly, apathy is the only awareness dimension, rather than the cognitive, relational,
15 emotional, behavioural and autonomy in daily living dimensions, discriminating healthy
16 controls, mild Alzheimer's patients and moderate-to-moderately-severe Alzheimer's patients.

17 The other discriminant dimensions were the cognitive, autonomy and behavioural dimensions,
18 which only distinguished patients from healthy controls.

19 Secondly, when using a risk factor (i.e. stage of the disease as measured by the MMSE) to
20 take into account its interactions with awareness of apathy, the only associated factor was the
21 MMSE score. Therefore, this score also appears as the best predictor of awareness of apathy
22 in our sample, explaining *alone* 17.62% of the variance.

1 This appears congruent with a previous study reporting that apathy scored by a relative or a
2 clinician was systematically associated with awareness whatever the dimension explored
3 when using the patient-caregiver discrepancy method [10].

4 Nevertheless, some studies [21-22] have reported that the MMSE was not a predictor of
5 behavioural disturbances, although their objectives (studying imagery, personality changes...)
6 and assessment tools were different from those used here which only partially concerned
7 apathy. Alongside, some authors such Starkstein et al. [2] clearly highlighted the associations
8 between increased dementia, increased apathy and decreased awareness with a longitudinal
9 methodology. Our results were totally congruent with that all the more so because the patient
10 groups were more impaired than the HC group for all the awareness scores and the apathy
11 scores.

12 Therefore, it can appear curious that in spite of our knowledge about the relationship between
13 apathy and awareness or apathy and dementia, there is no study assessing awareness of apathy
14 across different stages in Alzheimer's disease. For several years, anosognosia has been known
15 to be a predictor of apathy in Alzheimer's disease [4], and apathy is known to be a main risk
16 factor for conversion of Mild Cognitive Impairment into Alzheimer's disease [23-24].
17 Recently, Azocar et al. [5] reported that ten out of eleven studies on apathy and impaired
18 awareness found positive associations between them. In addition, systematic associations
19 between different domains of awareness as measured with the A-QD and apathy were also
20 reported by Amanzio et al. [25] and Mak et al. [26].

21 Indeed, we found one study on awareness of apathy among addiction patients [27]. This study
22 reported that greater grey matter volume in the dorsal striatum was associated with poorer
23 awareness of apathy among cocaine-dependent individuals. We found another study reporting
24 the role of awareness dimensions in AD [28]. This study showed that the level of awareness
25 differs according to the dimension studied, with awareness of the overall condition and

1 executive functions more strongly affected and relatively better preservation of awareness of
2 dis-inhibition and apathy. It is possible that the differing objectives, assessment tools and
3 statistical analyses used in this second study could explain why the authors did not report the
4 same findings as ours. Nevertheless, the lack of studies relating to awareness of apathy across
5 different stages of Alzheimer's disease could be explained by other behavioural disturbances
6 appearing with disease progression that could mask apathy. However, apathy is the
7 commonest symptom at any stage of the disease [6-7]. Awareness of it seems to increase with
8 disease progression and it therefore appears as a very discriminating dimension for awareness
9 assessment in Alzheimer's disease, in particular using the *patient-caregiver discrepancy*
10 method.

11 From a practical viewpoint, the AES, implementing the *patient-caregiver discrepancy*
12 method, can be used to assess awareness in mild to moderate stages of Alzheimer's disease
13 only, because of the several response choices (Never, Sometimes, Often, Always), making the
14 scale more difficult to complete in more severe stages of the disease. Other apathy scales
15 could be more suited to severe stages of the disease such as the *Apathy Inventory* designed on
16 the same principle as the AES, but comprising only three general questions relating to
17 affectivity, initiation and interest in each version (patient, relative and caregiver) [29].

18 Several limitations should be underlined. Group sizes were not matched and some of them
19 were small. [Nor were they matched for age or for education level, which could increase the](#)
20 [impact of MMSE on awareness of apathy as](#) the level of apathy. The depression scale was
21 only scored by participants, which does not take into account anosognosia towards depression
22 reported in AD [30] possibly explaining the comparability for depression across groups. There
23 was collinearity between the factors entered into the model, and the validity conditions for
24 linear models were not totally met, in particular for homoscedasticity. [Furthermore,](#)

1 adjustment on covariates could bias the variable selection strategy in the context of
2 collinearity.

3 Further studies should explore associations between apathy and lack of awareness in order to
4 determine whether lack of awareness is a main component of apathy, and to identify any
5 overlap between symptoms. Because apathy is a person's lack of concern towards his or her
6 environment and him or herself, greater apathy could lead to poorer awareness. Therefore,
7 one question remains: whether awareness of apathy could be a meta-awareness.

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