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Apathy is the best dimension to consider for awareness assessment in Alzheimer's disease

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Running title: *Awareness of apathy in Alzheimer's disease*

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 Introduction

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

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

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

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

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

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

2 Method

2.1 Participants

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

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

2.2 Evaluation tools

2.2.1 Cognitive assessment

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

2.2.2 Awareness assessment

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

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

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

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

2.2.3 Mood/behavioural assessments

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

2.3 Statistical analyses

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

3 Results

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

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

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

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

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

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

4 Discussion

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

Firstly, apathy is the only awareness dimension, rather than the cognitive, relational, emotional, behavioural and autonomy in daily living dimensions, discriminating healthy controls, mild Alzheimer's patients and moderate-to-moderately-severe Alzheimer's patients. The other discriminant dimensions were the cognitive, autonomy and behavioural dimensions, which only distinguished patients from healthy controls.

Secondly, when using a risk factor (i.e. stage of the disease as measured by the MMSE) to take into account its interactions with awareness of apathy, the only associated factor was the MMSE score. Therefore, this score also appears as the best predictor of awareness of apathy 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...) and
6 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

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

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

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

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

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

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5 References

[1] Starkstein SE (2014) Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex* **61**, 64-73.

[2] Starkstein SE, Jorge R, Mizrahi R, Robinson RG (2006) A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **77**(1), 8-11.

[3] Horning SM, Melrose R, Sulzer D (2014) Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *Int J Geriatr Psychiatry* **29**, 77-84.

[4] Starkstein SE, Brockman S, Bruce D, Petracca G (2010) Anosognosia Is a Significant Predictor of Apathy in Alzheimer's Disease. *J Neuropsychiatry Clin Neurosci* **22**, 378-383.

[5] Azocar I, Livingston G, Huntley J (2021) The Association Between Impaired Awareness and Depression, Anxiety, and Apathy in Mild to Moderate Alzheimer's Disease: A Systematic Review. *Front Psychiatry* **12**, 633081.

- 1 [6] Benoit M, Staccini P, Brocker P, Benhamidat T, Bertogliati C, Lechowski L, Tortrat D,
2 Robert PH (2003) Behavioral and Psychological Symptoms in Alzheimer's Disease: Results
3 from REAL.FR study. *Rev Med Interne* **24**(3), 319s-324s.
- 4 [7] Nobis L, Husain M (2018) Apathy in Alzheimer's disease. *Curr Opin Behav Sci* **22**,7-13.
- 5 [8] Mograbi DC, Morris RG (2014) On the relation among mood, apathy, and anosognosia in
6 Alzheimer's disease. *J Int Neuropsychol Soc* **20**(1), 2-7.
- 7 [9] Jacus JP, Mayelle A, Voltzenlogel V, Cuervo-Lombard CV, Antoine P (2020) Modelling
8 awareness in Alzheimer's disease. *J Alzheimers Dis* **76**, 89-95.
- 9 [10] Jacus JP, Voltzenlogel V, Mayelle A, Antoine P, Cuervo-Lombard CV (2021)
10 Awareness dimensions in Alzheimer's disease. *Rev Neurol* In Press.
- 11 [11] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk
12 WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P,
13 Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to
14 Alzheimer's disease: recommendations from the National Institute on Aging and the
15 Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease.
16 *Alzheimers Dement* **7**(3), 263-269.
- 17 [12] Folstein MF, Folstein SE, McHugh PR (1975) Mini Mental State. A practical method for
18 grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
- 19 [13] Hugonot-Diener L (2007) The Mini Mental Status Examination or MMSE consensual
20 version of GRECO. *Rev Geriatr* **32**(3), 225-229.
- 21 [14] Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: A frontal assessment
22 battery at bedside. *Neurology* **55**, 1621-1626.

- 1 [15] Ergis AM, Van der Linden M, Deweir B (1994) L'exploration des troubles de la
2 mémoire épisodique dans la maladie d'Alzheimer débutante au moyen d'une épreuve de
3 rappel indicé. *Rev Neuropsychol* **4**, 47-68.
- 4 [16] Barbeau E, Tramonì, E, Joubert S, Mancini J, Ceccaldi M, Poncet M (2004) *Evaluation*
5 *de la mémoire de reconnaissance visuelle: normalisation d'une nouvelle épreuve en choix*
6 *forcé (DMS 48) et utilité en neuropsychologie clinique*. In L'évaluation des troubles de la
7 mémoire M. Van Der Linden & le GRENEM eds. Solal, Marseille, pp. 85-101.
- 8 [17] Prigatano GP, Fordyce DJ (1986) Cognitive dysfunction and psycho-social adjustment
9 after brain injury. In *Neuropsychological rehabilitation after brain injury*, Prigatano GP, eds.
10 The Johns Hopkins University Press, Baltimore, pp. 96-118.
- 11 [18] Starkstein SE, Jorge R, Mizrahi R, Robinson RG (2006) A diagnostic formulation for
12 anosognosia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **77**, 719-725.
- 13 [19] Marin RS, Biedrzycki RC, Firinciogullari S (1991) Reliability and validity of the apathy
14 evaluation scale. *Psychiatry Res* **38**, 143-162.
- 15 [20] Clément JP, Nassif RF, Léger JM, Marchan F (1997) Development and contribution to
16 the validation of a brief French version of the Yesavage Geriatric Depression Scale.
17 *Encephale* **23**(2), 91-99.
- 18 [21] Ott BR, Noto RB, Fogel BS (1996) Apathy and loss of insight in Alzheimer's disease: a
19 SPECT imaging study. *J Neuropsychiatry Clin Neurosci* **8**(1), 41-46.
- 20 [22] Bózzola FG, Gorelick PB, Freels S (1992) Personality changes in Alzheimer's disease.
21 *Arch Neurol* **49**(3), 297-300.

- 1 [23] Vicini Chilovi B, Conti M, Zanetti M, Mazzù I, Rozzini L, Padovani A (2009)
2 Differential impact of apathy and depression in the development of dementia in mild
3 cognitive impairment patients. *Dement Geriatr Cogn Disord* **27**(4), 390-398.
- 4 [24] Geda YE, Rocca WA, Knopman DS, Pankratz SV, Roberts RO, Petersen RC (2007)
5 Apathy is a better predictor of mild cognitive impairment than depression: A population based
6 study. *Alzheimers Dement* **3**(3), S139.
- 7 [25] Amanzio M, Vase L, Leotta D, Miceli R, Palermo S, Geminiani G (2013) Impaired
8 awareness of deficits in Alzheimer's disease: the role of everyday executive dysfunction. *J Int*
9 *Neuropsychol Soc* **19**, 63–72.
- 10 [26] Mak E, Chin R, Ng LT, Yeo D, Hameed S (2015) Clinical associations of anosognosia in
11 mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry* **30**, 1207–1214.
- 12 [27] Moreno-López L, Albein-Urios N, Martínez-González JM, Soriano-Mas C, Verdejo-
13 García A (2017) Neural correlates of impaired self-awareness of apathy, disinhibition and
14 dysexecutive deficits in cocaine-dependent individuals. *Addict Biol* **22**(5), 1438-1448.
- 15 [28] Bertrand E, Mograbi DC, Brown RG, Landeira-Fernandez J, Morris RG (2019)
16 Heterogeneity of Anosognosia in Alzheimer's Disease According to the Object of Awareness.
17 *Psychology & Neurosciences*, **12**(2), 282–290.
- 18 [29] Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, Caci H, Borg M,
19 Brocker P, Bedoucha P (2002) The Apathy Inventory: assessment of apathy and awareness in
20 Alzheimer's disease Parkinson's disease and Mild cognitive impairment. *Int J Geriatr*
21 *Psychiatry* **17**(12), 1099-1105.
- 22 [30] Verhülsdonk S, Quack R, Höft B, Lange-Asschenfeldt C, Supprian T (2013)
23 Anosognosia and depression in patients with Alzheimer's dementia. *Arch Gerontol Geriatr*
24 **57**, 282-287.