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Modelling awareness in Alzheimer's disease

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Running title: Modelling awareness in Alzheimer's disease

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1 **Abstract**

2 This study aimed to provide a model of awareness in Alzheimer's disease using the stage of
3 the disease as a risk factor. Awareness was assessed using three methods (patient-caregiver
4 discrepancy, prediction-performance discrepancy, clinical rating). Twenty-five healthy
5 control subjects and sixty-one patients participated, with measures of cognition, apathy,
6 depression and awareness. These measures were introduced into a manual backward
7 regression. Confounding factors impacting at least 15% of the exposure factor estimate were
8 maintained in the model. Except for the prediction performance discrepancy, also presenting
9 cognitive associations, the other awareness assessments suggested a major role of
10 depression and apathy as impacting factors.

11 **Key Words:** Alzheimer's disease, Apathy, Awareness, Depression

12

1 Introduction

2 Awareness in Alzheimer's Disease (AD) is a broad and changing construct, varying with
3 different approaches and the stage of the disease. These approaches mainly distinguish (1)
4 explicit and (2) implicit measures, based on three methods usually used to assess awareness:
5 (1a) *patient-caregiver discrepancy*, (1b) *prediction of performance discrepancy*, and (2)
6 *clinical rating* [1-2]. Our objective was the development of a model of awareness in AD
7 based on the different approaches of this phenomenon and disease severity.

8 Most studies reported increased frequency of impaired awareness as the disease progresses,
9 so that disease severity appears as the main risk factor for impaired awareness [1, 3-4].
10 These studies also reported specific associations with cognitive and behavioral executive
11 dysfunctions [4-6]. Recent research found negative correlations with depression and positive
12 associations with apathy. These associations were observed using the *patient-caregiver*
13 *discrepancy method* [6]. Other associations, particularly with executive functions, were
14 observed using the *prediction of performance discrepancy method* [7].

15 However, many awareness studies have produced contrasted results due to these different
16 methodologies or different stages of the disease [3-5]. Furthermore, these
17 studies frequently used stepwise regression analyses, which are more suited to providing
18 predictors of a phenomenon than to reflecting relationships between the phenomenon (for
19 instance awareness) and risk factors (e.g. the stage of AD), so as to model that
20 phenomenon. Indeed stepwise regression analyses do not consider confounding factors.
21 Confounders are not significant factors, but their removal impacts the exposure factor
22 estimate without interacting with it. Thus, removing a confounding variable can bias the risk

factor coefficient estimate. A multivariate analysis using an exposure (risk) factor appears as better suited to modeling the relationship between awareness and the exposure factor if the different factors involved in the phenomenon (apathy, depression, executive functions, etc.) are tested as potential confounders [8-9].

Our study aimed to investigate the relationship between awareness and AD severity, taking into account different approaches to awareness. We hypothesized that apathy and depression would be significantly involved across the different approaches, whereas confounding factors would be more specific to a single approach or assessment method.

Materials and method

Participants

Eighty-six – 86 participants took part in the study. Twenty-five – 25 were Healthy Controls (HC) recruited from a pool of participants and senior-citizen associations. They had no memory complaint and scored normally on a background assessment using the *Mini Mental State Examination* – MMSE [10-11], the *Free and Cued Recall test* – FCRT [12-13], the *Delayed Match to Sample test* [14] and the *Frontal Assessment Battery* – FAB [15]. Sixty-one – 61 participants were patients recruited from a memory center. They were diagnosed by a senior neurologist and a neuropsychologist (JP. J) for probable AD according to the recommendations of the National Institute on Aging and the Alzheimer's Association working group on diagnostic guidelines for AD [16]. The stage of the disease was determined using the MMSE score (mild to moderately severe) [17]. All participants signed consent to participate and this study was approved by the local ethics committee.

1 Evaluation tools

2 Additional factor assessments

3 We assessed three additional factors usually involved in awareness: (1) Depression with the
4 *Geriatric Depression Scale* [18] (GDS) - the higher the score, the higher the level of
5 depression ; (2) Apathy with the *Apathy Evaluation Scales* [19] (scored by a relative:
6 $AES_{Relative}$ and the clinician: $AES_{Clinician}$) - higher scores indicate lesser apathy - and (3)
7 Autonomy with the *Instrumental Activity of Daily Living* scale (IADL) scored by a relative [20]
8 - the greater the autonomy, the higher the score.

9 Awareness assessments

10 As indicated above, four measures derived from the three assessment methods were used
11 to assess awareness.

12 Concerning *patient-caregiver discrepancy*, we used (1) the *Patient Competency Rating Scale*
13 – PCRS [21] and (2) the *Anosognosia Questionnaire for Dementia* – A-QD [22]. (1) The PCRS
14 requires the participant and a relative to answer the same 30 questions on the participant's
15 ability to perform various tasks of daily living, with particular reference to emotional control.
16 The level of awareness is assessed by subtracting the participant rating from the relative
17 rating. A negative score indicates poorer awareness. (2) The A-QD is based on the same
18 principle as the PCRS, but mainly concerns memory and behavioral disturbances in AD. A
19 positive score indicates poorer awareness.

20 Concerning the *prediction of performance discrepancy*, we used the *Multidimensional*
21 *Isomorphic Simple Awareness Assessment* – MISAware [7]. Here, the participant is asked to
22 predict his(her) neuropsychological performance (correct / incorrect) on the *Dementia*

1 *Rating Scale* [23]. The subjective self-ratings are then compared with those actually
2 obtained. The poorer the awareness the higher the score.

3 Finally concerning the *clinical rating*, the *Self-Consciousness Scale in AD* – SCSAD – was used
4 only with patients because inappropriate for HC [6, 24]. The SCSAD is a structured patient
5 interview including fourteen questions in seven domains: identity, knowledge of cognitive
6 disturbances, affective state, bodily representation, prospective memory, introspection
7 abilities, and moral judgments. The better the awareness the higher the score.

8 **Statistical analyses**

9 The statistical analyses were carried out using R software (version 3.6.1.) with the Hmisc
10 package. As the HC group comprised fewer than 30 subjects, approximation with a Gaussian
11 distribution was not possible and non-parametric tests were used to compare the
12 performances between HC and patients.

13 A multivariate regression analysis was performed on the patient group (n=61). We
14 performed a backward manual regression for each of the four global measures of
15 awareness, using the following variable selection method [8-9]:

16 The MMSE score was used as the exposure factor determining the stage of AD [9] and was
17 maintained in the model even if it was non-significant. Demographics (age, educational level
18 in years, gender), autonomy (IADL), executive functioning (FAB), apathy (AES) and
19 depression (GDS) were univariately tested with each of the four global measures of
20 awareness (dependent variable). The cut-off was set at $p < 0.25$ for this preliminary model to
21 avoid excluding future significant variables. Each interaction between the exposure factor
22 (MMSE) and the variables retained in the preliminary model was univariately tested with the

dependent variable. The cut-off was set at $p < 0.05$. Once the preliminary model was established with the selected interactions, the backward process began, removing one by one the non-significant interactions ($p < 0.05$), beginning with those having the highest p -values. The same process was performed with the non-significant main factors ($p < 0.05$). When removal impacted at least 15% of the exposure factor estimate (relative variation), the factor was considered as a potential confounder and was therefore maintained in the model, knowing that this relative variation is significant as it falls between 10 to 20% [8]. The analysis was discontinued when there were no remaining significant factors. Confounding factors and the exposure factor (MMSE) remained in the final model. Finally, we ascertained that confounding variables were not effect-modifiers by testing their interactions with the exposure factor ($p < 0.05$).

Results

Comparisons between HC and patients

HC were younger ($W=275.5$, $p < 0.0001$) and more educated than patients ($W=1127.5$, $p=0.0005$). The groups were matched for gender ($\chi^2=0.0396$, $p=0.8422$). HC performed better than patients for all cognitive variables including autonomy (MMSE, FAB and IADL: $p < 0.0001$). They were less apathetic (AES_{Relative} and AES_{Clinician}: $p < 0.0001$) and less depressed than patients ($W=545$, $p=0.0368$).

Concerning awareness, *patient-caregiver discrepancy* data showed a significant group effect on the PCRS ($W=1157$, $p < 0.0002$ [HC>AD]), and on the A-QD ($W=382$, $p=0.0003$ [HC<AD]).

Concerning *prediction of performance discrepancy*, the MISAware data showed a significant

1 group effect ($W=61$, $p<0.0001$, [HC<AD]). Thus HC were more aware than patients on all the
2 awareness scales (Table 1).

3 On the whole sample, and in the patients group, all the awareness scales correlated one to
4 another, except the SCSAD with the PCRS ($p=0.0564$) and with the A-QD ($p=0.0719$) (the p-
5 values are the same because the SCSAD was used only with the patient group).

6 On the whole sample, and in the patients group, all the variables (age, educational level,
7 MMSE, BREF, IADL, AES_{Relative}, AES_{Clinician}), correlated one to another ($p<0.01$ because of the
8 number of variables), except for depression (GDS) which did not correlate with any other.

9 Regression analyses

10 Using the exposure factor (MMSE), demographic data (age, educational level, gender), and
11 the available variables (IADL, FAB, GDS, AES_{Relative} and AES_{Clinician}), we ran four models with
12 the patient group only (one for each awareness scale used), because of differences in
13 awareness between the groups and in order to model awareness in AD (Table 2).

14 The first model involving the PCRS comprised the MMSE, IADL, GDS, AES_{Relative} and gender.
15 Here the PCRS score was mainly explained by the GDS score ($\beta=3.71$, $p<0.0001$) and the
16 AES_{Relative} score ($\beta=0.89$, $p=0.0002$). The IADL score ($\beta=2.13$) and the gender ($\beta=-6.56$) were
17 confounding factors and non-significant ($p>0.05$). The exposure factor (MMSE: $\beta=-1.09$) was
18 non-significant ($p>0.05$).

19 The second model involving the A-QD included the MMSE, IADL, GDS and AES_{Relative} scores.
20 Here the A-QD score was mainly explained by the GDS score ($\beta=-2.36$, $p=0.0001$) and the
21 AES_{Relative} score ($\beta=-0.61$, $p=0.0001$). The IADL score ($\beta=-1.31$) was confounding factor and
22 non-significant ($p>0.05$). The exposure factor (MMSE: $\beta=0.45$) was non-significant ($p>0.05$).

The third model involving the SCSAD included the MMSE, FAB, GDS, AES_{Relative} and AES_{Clinician} scores. Here the SCSAD was mainly explained by the GDS score ($\beta=0.28$, $p=0.0022$) and the AES_{Clinician} score ($\beta=0.09$, $p=0.0168$). The FAB ($\beta=0.09$) and the AES_{Relative} scores ($\beta=0.04$) were confounding factors and non-significant ($p>0.05$). The exposure factor (MMSE: $\beta=0.01$) was not significant ($p>0.05$).

The fourth model involving the MISAware comprised the MMSE, IADL, FAB, and AES_{Relative} scores. Here the MISAware was mainly explained by the MMSE ($\beta=-0.53$, $p=0.0178$), the FAB ($\beta=-1.24$, $p<0.0001$) and the AES_{Relative} scores ($\beta=-0.17$, $p=0.0325$). The IADL score ($\beta=1.06$) was confounding factor and non-significant ($p>0.05$).

None of the confounding variables were effect modifiers in any model.

For all models, residuals analyses showed normal fit: Shapiro test for the PCRS: $W=0.9711$, $p=0.1578$; for the A-QD: $W=0.9761$, $p=0.2766$; for the SCSAD: $W=0.9647$, $p=0.0757$; and for the MISAware: $W=0.9691$, $p=0.126$. Linearity and homoscedasticity were satisfactory: Snedecor test for the PCRS: $F_{1-0.05}^{60,60}=0.8857$, $p=0.6399$; for the A-QD: $F_{1-0.05}^{60,60}=0.8267$, $p=0.4633$; for the SCSAD: $F_{1-0.05}^{60,60}=0.6435$, $p=0.0904$; and for the MISAware: $F_{1-0.05}^{60,60}=0.9165$, $p=0.7367$ (Figure 1).

Discussion

These results suggest that apathy and depression are significantly linked to awareness as measured in the different approaches, whatever the stage of the disease. Horning et al. [4] reported that more intact insight was related to anxiety and depressed mood, whereas impaired insight was related to greater apathy, after adjusting their regression analyses on the MMSE. Our results show that this can be considered as independent from the

assessment method. Nevertheless, our hypotheses are not totally validated. Firstly, perfect homogeneity of awareness cannot be argued from these results because one assessment method (MISAware) was not mainly explained by depression but by cognitive factors and apathy. Secondly, the confounders were globally similar across approaches and no factors specific to each awareness approach were found. Thus, our results show homogeneity overall, but certain heterogeneities in awareness measures in AD.

Our results could suggest that the nature of the factors found to be associated (affective and behavioral or cognitive) depends on the referential used to assess awareness (human or test rating). Thus, It is likely that different awareness phenomena are captured according to the referential used [5]. Thus in clinical practice, choosing an awareness measure should be based more on practical aspects than on anything else, each method being here sensitive to AD. Although considered to be more reliable [1, 25], the *patient-caregiver discrepancy* method appears difficult to use in the moderate stages of AD (several response formats, items addressed to patients living at home, etc.), whereas *prediction of performance discrepancy* (using a dementia scale) and the *clinical rating* methods seem more suited to this.

Preventive action could also be undertaken on depression and on apathy to maintain awareness of deficits as comfortably as possible for the patients, since its impairment can result in a loss of autonomy, widely contribute to the caregiver's burden and finally lead to early placement in a structured living environment [4-6].

Several limitations should however be underlined. Patients and HC were not matched for group size and the patient sample size could be criticised in relation to our statistical strategy derived from epidemiological methods. There was collinearity between the factors

entered into the model, and the model did not reflect all the variables known to be involved in awareness. Nevertheless, all models complied with the validity conditions for linear models. Additional research on awareness in AD is required to confirm this and explore a possible depression-apathy continuum, using longitudinal methodologies.

The authors have no conflict of interest to report.

Word count: 2057 words.

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1 **Table 1:** Demographic, cognitive, behavioral and awareness data across the groups

	Variables	HC (n=25)	Patients (n=61)	Statistics	p
		Med. (min;max)	Med. (min;max)		
Demographic	Age (years)	73 (61;85)	82 (62;92)	W=275.5*	<0.0001 ^a
	Education (years)	14 (8;20)	10 (6;18)	W=1127.5*	0.0005 ^b
	Gender (% female)	56.00	50.8	$\chi^2=0.0396^{**}$	0.8422
Cognitive	IADL	8 (8;8)	6 (3;8)	W=1400*	<0.0001 ^a
	MMSE	29 (26;30)	23 (13;28)	W=1485*	<0.0001 ^a
	BREF	17 (15;18)	13 (6;18)	W=1345.5*	<0.0001 ^a
Behavioral / mood	GDS	3 (0;10)	4 (0;11)	W=545*	0.0368 ^b
	AES relative	64 (43;72)	45 (25;68)	W=1359*	<0.0001 ^b
	AES clinician	67 (53;72)	49 (33;67)	W=1478*	<0.0001 ^b
Awareness	PCRS	2 (-17;22)	-12(-55;45)	W=1157*	0.0002 ^b
	AQ-D	-5 (-19;10)	5 (-23;37)	W=382*	0.0003 ^a
	MISAware	0 (0;4)	9 (0;35)	W=61*	<0.0001 ^a
	Self Consciousness	---	23 (20;27)	---	---

2 * Mann & Whitney test ; **Chi squared test.

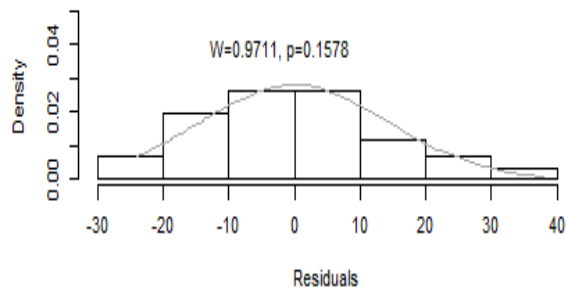
3 ^a HC<AD ; ^b HC>AD

Scales		Factors	β	IC95% β	p
Model 1	PCRS	Mini-Mental State Examination _a	-1.09	-2.32 ; 0.15	0.0894
		Instrumental Activity of Daily Living _b	2.13	-1.00 ; 5.26	0.1883
		<i>Geriatric Depression Scale</i>	<i>3.71</i>	<i>2.10 ; 5.33</i>	<i><0.0001</i>
		<i>Apathy scored by the relative</i>	<i>0.89</i>	<i>0.45 ; 1.32</i>	<i>0.0002</i>
		Sexe (female) _b	-6.56	-14.3 ; 1.26	0.1062
Model 2	AQ-D	Mini-Mental State Examination _a	0.45	-0.35 ; 1.25	0.2704
		Instrumental Activity of Daily Living _b	-1.31	-3.41 ; 0.79	0.2262
		<i>Geriatric Depression Scale</i>	<i>- 2.36</i>	<i>-3.43 ; -1.28</i>	<i>0.0001</i>
		<i>Apathy scored by the relative</i>	<i>-0.61</i>	<i>-0.90 ; -0.32</i>	<i>0.0001</i>
Model 3	Self Consciousness Scale	Mini-Mental State Examination _a	0.01	-0.12 ; 0.14	0.9092
		Frontal Assessment Battery _b	0.09	-0.08 ; 0.25	0.3176
		<i>Geriatric Depression Scale</i>	<i>0.28</i>	<i>0.11 ; 0.45</i>	<i>0.0022</i>
		Apathy scored by the relative	0.04	-0.01 ; 0.09	0.1214
		<i>Apathy scored by the clinician</i>	<i>0.09</i>	<i>0.02 ; 0.16</i>	<i>0.0168</i>
Model 4	MISAware	<i>Mini-Mental State Examination _a</i>	<i>-0.53</i>	<i>-0.96 ; -0.10</i>	<i>0.0178</i>
		Instrumental Activity of Daily Living _b	1.06	-0.03 ; 2.15	0.0614
		<i>Frontal Assessment Battery</i>	<i>-1.24</i>	<i>-1.79 ; -0.70</i>	<i><0.0001</i>
		<i>Apathy scored by the relative</i>	<i>-0.17</i>	<i>-0.32 ; -0.02</i>	<i>0.0325</i>

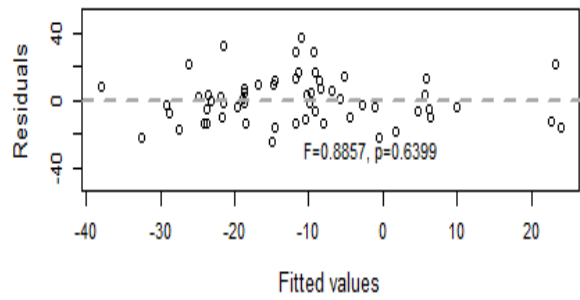
1 Table 2: Regression models for awareness scales in patient group

- 1 ^a Exposure factor (maintained even if it was not significant); ^b Confounding factors (when
- 2 removal impacted at least 15% of the exposure factor estimate, therefore kept in the model
- 3 although not significant); **Significant variables**.
- 4 Figure 1: Plots of normality and homoscedasticity for each model

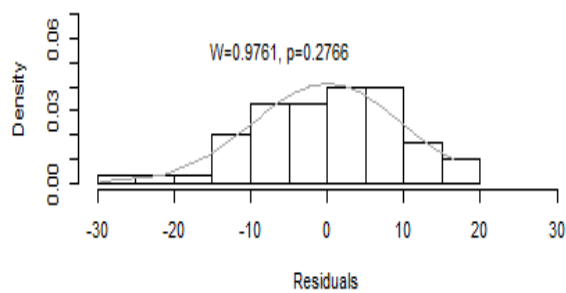
PCRS: histogram of residuals



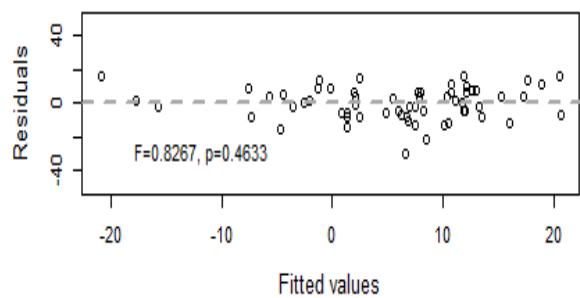
PCRS: homoscedasticity between residuals and fitted values



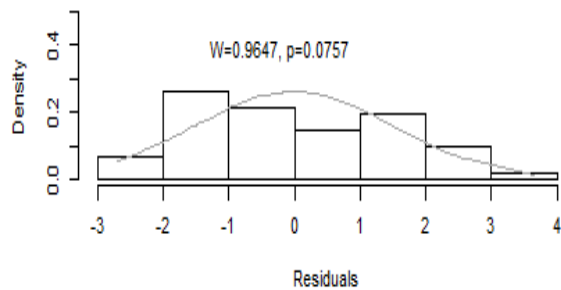
AQ-D: histogram of residuals



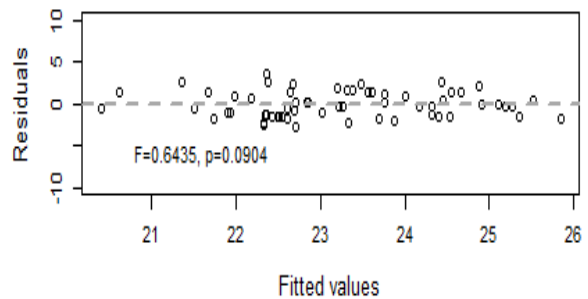
AQ-D: homoscedasticity between residuals and fitted values



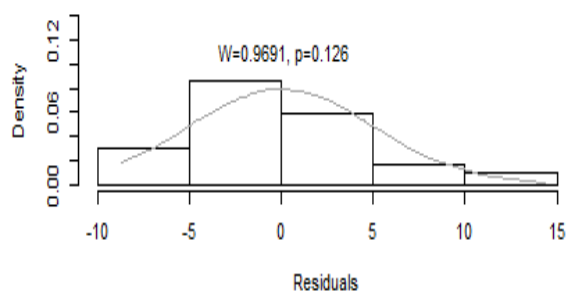
Self: histogram of residuals



Self: homoscedasticity between residuals and fitted values



MISAware: histogram of residuals



MISAware: homoscedasticity between residuals and fitted values

