Awareness dimensions and associated factors in Alzheimer's disease

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ABSTRACT

Objectives – We recently reported the major role depression and apathy in awareness among Alzheimer patients, using the stage of the disease as an exposure factor and exploring different assessment methods. Using the same patient data, we aimed here to explore the different dimensions of awareness assessed by different sub-scales in awareness scales.

Method – Sixty-one Alzheimer patients were examined using four awareness scales relating to three assessment methods: (a) *patient-caregiver discrepancy*; (b) *clinical rating*; and (c) *prediction of performance discrepancy*. Global cognition, executive functioning, autonomy, depression and apathy were also assessed. Multivariate logistic models were performed using disease stage as an exposure factor for awareness scales and sub-scales. Correlations across the different factors and patient and caregiver awareness ratings were computed.

Results – The *patient-caregiver discrepancy* and *clinical rating* methods (a, b) both identified the factors associated with awareness in the overall scales and the sub-scales as being depression and/or apathy. Depression correlated with patient self-ratings while apathy correlated with caregiver ratings. The *prediction of performance discrepancy* method (c) identified different factors in the overall scale, executive factors in three sub-scales involving executive domains and the memory factor in a sub-scale involving the mnesic domain.

Discussion – The awareness scales using a referential based on a human rating (a, b) suggest that awareness is unidimensional, with depression impacting self-reports and apathy influencing caregiver/clinical reports. Scales based on a test rating (c) appear to be more closely associated with the dimensions assessed. This highlights the role of the reference system for awareness assessment in Alzheimer's disease.

KEY WORDS – Alzheimer's disease, Apathy, Awareness assessment method, Awareness dimensions, Depression.

1 INTRODUCTION

Awareness disturbances are core features in Alzheimer's disease (AD) prematurely affecting patient autonomy and causing early placement in structured living environments [1]. This symptomatology is heterogeneous and various terms to refer to different conceptualizations have been used to describe it [2]. Anosognosia was the first term used. It involves cognitive conceptualizations suggesting a main role of metacognition in this phenomenon [3]. Denial is more often used in psychoanalytical conceptualizations, in reference to the unconscious refusal to acknowledge a too painful reality [4]. Insight, especially in its broader form, is a psychiatric viewpoint involving judgments and the nature of patients' consciousness of their disorders, in particular delusions and hallucinations. In its narrower form ("*insight into dementia*"), awareness is conceptualized as the basic perception of impairments [5]. Other conceptualizations have been proposed, but it is known that none of them are able to explain the heterogeneity of awareness disturbances in AD [6]. This is why Clare and colleagues [6] developed a bio-psychosocial model suggesting that awareness disturbances relate to a self-adjustment as resulting from biological, psychological and social changes with the progress of the disease. Subsequently phenomenological models have considered the disease experience expressed by the patient in order to take the heterogeneity of awareness into account by way of different mechanisms or processes (comparison between past and present, metacognition, etc.), domains (communication, memory, autonomy, etc.) and modes of expression (denial, bewilderment, causal attribution, etc.) [7].

Except for bio-psychosocial and phenomenological approaches, awareness in AD is classically assessed using three methods [8]. The *patient-caregiver discrepancy* method, using the caregiver ratings as the reference by subtracting the patient ratings from them. The scales using this method explore different domains or dimensions of awareness, such as cognitive or behavioural disturbances. The *clinical rating* method use a structured interview with the

patient concerning different domains of impairment in which the clinician rating is used as the reference. The *prediction of performance discrepancy* method in which the scores obtained on the test used are the reference to be compared to the predictions. The domains of awareness explored are those of the test used.

These three methods mainly focus on awareness dimensions, which are presented as the first aspect to consider to understand patients with impaired awareness of their disorder [8]. However, using these methods, many studies have reported heterogeneous results, attributed mainly to the different assessment methods, domains of awareness and disease stages studied [5]. Alongside, awareness seems to be associated with disease stage [9]. In a previous study [1], we recently suggested a model of awareness in AD using disease severity as an exposure factor (risk factor of impaired awareness) and integrating these three main assessment methods. The results showed that greater awareness was associated with greater depression and lower apathy for all the scales relating to the *patient-caregiver discrepancy* and *clinical rating* methods. Greater awareness was associated with more heterogeneous factors (apathy and especially cognition) in the *prediction of performance discrepancy* method.

Nevertheless, these results did not take into account the role of the different dimensions of awareness (i.e. the different sub-scales or dimensions included in each scale used). Because awareness is heterogeneous, one disturbance can be recognized while another can be misunderstood by the patient, and thus it is relevant to take into account their impact in daily living. Therefore, using the same patient data as in our previous study [1], our objective was here to evaluate the role of these dimensions and their associated factors.

Considering the heterogeneity of awareness disturbances in AD [1, 5, 8], we hypothesized that in addition to the factors (apathy-depression in particular) usually associated with global awareness scores [1, 9-10], there would be specific factors associated with the different awareness dimensions (i.e. a cognitive awareness sub-scale will be associated with cognitive

functions, a subtest on awareness of activity of daily living abilities will be associated with autonomy in daily living, and so on).

2 MATERIALS AND METHOD

2.1 Participants

Sixty-one Alzheimer patients (mean age=81.3; % female=50.8) recruited from a memory clinic and diagnosed following the National Institute for Aging and the Alzheimer's Association working group recommendations [11] were included in this study. They constituted the patient group of our previous study [1] that also included healthy controls.

2.2 Evaluation tools

AD patients were assessed using four awareness scales related to the three main assessment methods presented above [1, 9].

(a) For the patient-caregiver discrepancy method:

– The *Patient Competency Rating Scale* – PCRS [12] including the sub-scales: "*Activities of Daily living (ADL)*", "*Cognition*", "*Interpersonal Relations*" and "*Emotions*". The PCRS 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. Positive scores indicate greater awareness.

– The *Anosognosia Questionnaire for Dementia* – A-QD [13] 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 negative scores indicate greater awareness.

(b) For the clinical rating method, we used the *Self-Consciousness Scale in AD* – SCSAD [14], a structured patient interview involving seven dimensions of self-consciousness: "*Identity*", "*Cognitive disturbances*", "*Affective state*", "*Bodily representation*", "*Prospective memory*", "*Introspection abilities*" and "*Moral judgments*". Higher scores indicate greater awareness.

(c) For the *prediction of performance discrepancy* method, we used the *Multidimensional Isomorphic Simple Awareness Assessment* – MISAware [15] which requires participants to predict their neuropsychological performance on the *Dementia Rating Scale* – DRS [16]. The self-ratings are then compared to those obtained on the DRS, which includes five sub-scales: "*Attention*", "*Initiation*", "*Conceptualization*" relating to executive functioning, "*Construction*" relating to visuo-spatial functioning, and "*Memory*" relating to mnesic functioning. Lower scores indicate greater awareness.

AD patients also completed the *Mini Mental State Examination* – MMSE [17-18] and the *Frontal Assessment Battery* – FAB [19] for cognitive performances. We used the *Instrumental Activities of Daily Living scale* – IADL [20], scored by a relative, to assess autonomy. Most patients (n=55) were also evaluated using the *Free and Cued Recall Test* – FCRT [21], assessing episodic memory. For all tasks, higher scores indicate better abilities.

Levels of depression and apathy, known to be involved in awareness in AD, were assessed [9]. We used the *Geriatric Depression Scale* – GDS (completed by the patient) [22], in which higher scores indicate greater depression, and the *Apathy Evaluation Scale* – AES [23] (completed by a relative: $AES_{Relative}$ and the clinician: $AES_{Clinician}$), in which lower scores indicate greater apathy.

2.3 Statistical analyses

The statistical analyses were carried out using R software (version 4.0.2) (generalhoslem, Hmisc, and questionr packages). In order to identify the factors associated with the different

awareness scales or sub-scales and disease stage, we performed a backward manual regression for each of them, using the following variable selection method [1-24]. To perform the regressions there must be no missing data. The MMSE score was used as the exposure factor determining the stage of AD [1, 18] and was always maintained in the model. Demographics (age, educational level in years and gender), autonomy (IADL), executive functioning (FAB), apathy (AES) and depression (GDS) were univariately tested with each of the four global measures of awareness and for each of their sub-scales or dimensions. The cut-off was set at $p<0.25$ for this preliminary model in order to avoid excluding future significant variables. Each interaction between the exposure factor (MMSE) and the variables retained in the preliminary model was univariately tested with the dependent variable. The cut-off was also set at $p<0.25$. 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. If an interaction was found to be significant, therefore the factor interacting with the exposure factor was maintained in the model even if it was non-significant. The same process was performed with the non-significant main factors ($p<0.05$). When removal of a main factor impacted at least 15% of the exposure factor estimate (relative variation: $\frac{adjusted\ estimate - crude\ estimate}{adjusted\ estimate}$), the factor was considered as a potential confounder and was therefore maintained in the model, given that this relative variation is significant when it falls between 10 and 20% [1]. The analysis was discontinued when there were no remaining significant factors. Confounding factors and the exposure factor (MMSE) remained in the final model. Because some sub-scales did not comply with the validity conditions for linear models, we used logistic multivariate models, setting a cut-off at the median value of the sample for each dependent variable[a] (overall

[a] Given that a logistic model is by definition binary.

awareness scales and sub-scales). Finally, we ascertained each model by the Hosmer and Lemeshow test (χ^2 non-significant)[b].

Because the conditions of parametric correlations (Pearson) were not fulfilled, we calculated non-parametric correlations between the available variables and predictions on the MISAware as well as self and caregiver's awareness reports, in order to have a better understanding of the logistic models.

3 RESULTS

We reported in Table 1 the demographic, cognitive, behavioural and awareness patient data.

3.1 Logistic models for the overall awareness scales and sub-scales

These models are presented in Table 2.

Because logistic models were used in the present study while we used linear models in our previous study [1], we checked that there were globally the same associations with the overall awareness scales.

While the total PCRS scores evidenced associations with the GDS and $AES_{Relative}$ in our previous study using a linear model [1], the total score was here associated with the same factors and the MMSE using a logistic model (GDS: OR=0.52, CI95%=0.32–0.75, p=0.002; $AES_{Relative}$: OR=0.89, CI95%=0.81–0.96, p=0.005; MMSE: OR=1.26, CI95%=1.02–1.60, p=0.004). All the PCRS sub-scales were associated with the GDS and/or the $AES_{Relative-Clinician}$. However, the "*Interpersonal Relations*" logistic model did not comply with the Hosmer and Lemeshow test (χ^2=16.48, p=0.03).

While the total A-QD score evidenced associations with the GDS and $AES_{Relative}$ in our previous study using a linear model [1], the total score remained associated with the same

[b] The Hosmer–Lemeshow test is a statistical test for goodness-of-fit for logistic regression models.

factors using a logistic model. Nevertheless, only the "*Cognition*" sub-scale was associated with the GDS and the $AES_{Relative}$. For the "*Behavioral disturbances*" sub-scale, there was merely a significant trend for both GDS and $AES_{Relative}$ (OR=0.76, CI95%=0.55–0.99, p=0.059; OR=0.94, CI95%=0.87–1.00, p=0.066 respectively).

Only three of the seven dimensions in the SCSAD proved discriminant and were useable: "*Cognitive disturbances* ", "*Introspection abilities*" and "*Moral judgments*". The others showed no variance and always reached the top scores.

While the total SCSAD score evidenced associations with the GDS and $AES_{Clinician}$ in our previous study using a linear model [1], the total score was here only associated with the $AES_{Relative}$ and the $AES_{Clinician}$ using a logistic model ($AES_{Relative}$: OR=0.89, CI95%=0.80–0.97, p=0.019; $AES_{Clinician}$: OR=0.87, CI95%=0.74–0.99, p=0.050). The three available dimensions were associated with the GDS and/or the $AES_{Relative\text{-}Clinician}$ and also with demographic variables.

While the total MISAware evidenced associations with the MMSE, $AES_{Relative}$ and FAB in our previous study using a linear model [1], the total score was here significantly associated with the MMSE, $AES_{Relative}$ and gender (female) using a logistic model (MMSE: OR=0.68, CI95%=0.51–0.85, p=0.002; $AES_{Relative}$: OR=0.84, CI95%=0.72–0.94, p=0.003; gender (female): OR=0.52, CI95%=1.19–2.85, p=0.038). The "*Attention*", "*Initiation*" and "*Conceptualization*" sub-scales were associated solely with the FAB, except for the "*Attention*" sub-scale, also significantly associated with age. The analysis failed to show significant factors associated with the "*Construction*" and "*Memory*" sub-scale scores. Nevertheless, in a complementary analysis introducing the FCRT (administered only to 55 patients), we observed that the "*Memory*" sub-scale showed a significant association with total recall (p=0.020), the GDS (p=0.040) and interactions between GDS and MMSE (p=0.033).

3.2 Non-parametric correlations (Table 3)

For non-parametric correlations across the available factors, including self/relative reports for PCRS, A-QD and MISAware predicted scores, the significance cut-off was set at $p<0.01$ because there were twenty-five (25) correlations. The predicted MISAware scores correlated with the MMSE and $AES_{Clinician}$ ($\rho=0.46$, $p=0.0002$; $\rho=0.35$, $p=0.0062$ respectively). Relative reports for the PCRS and for A-QD correlated with IADL ($\rho=0.46$, $p=0.0002$; $\rho=-0.41$, $p=0.0010$ respectively), $AES_{Relative}$ ($\rho=0.61$, $p<0.0001$; $\rho=-0.66$, $p<0.0001$ respectively) and $AES_{Clinician}$ ($\rho=0.33$, $p=0.0099$; $\rho=-0.33$, $p=0.0087$ respectively). Finally, self-reports for the PCRS and A-QD correlated solely with the GDS ($\rho=-0.58$, $p<0.0001$; $\rho=0.45$, $p=0.0003$ respectively).

4 DISCUSSION

Our present results show that the linear models used in our previous study [1] and the subsequent logistic models found the same overall associations with only minor differences.

Concerning both the *patient-caregiver discrepancy* and the *clinical rating* methods, our results suggest that, whatever the domain assessed, greater awareness is associated with greater depression and/or lower apathy. Contrary to our hypothesis relating to the role of specific factors associated with the domains assessed, cognitive awareness sub-scales did not show any associations with cognitive functions, such as the MMSE or FAB scores, when using these methods.

Concerning the *prediction of performance discrepancy*, the total MISAware scores did not evidence the same associations as three of its sub-scales (MMSE, gender and apathy versus executive functioning measured with the FAB only for "*Attention*", "*Initiation*" and "*Conceptualization*"). Two sub-scales showed no associations, but after introducing an additional explanatory variable assessing episodic memory measured by the FCRT,

associations with the "*Memory*" sub-scale were observed. This suggests that awareness could be associated with specific domains assessed by different sub-scales, highlighting the importance of awareness dimensions when using this method.

Our results still suggest a distinction between a referential based on a test rating and another based on a human rating (clinician or relative). This was suggested in our previous study [1] and seems to be congruent here, using only patient data for overall awareness scales and sub-scales. The referential based on a test rating seems relatively congruent with cognitive models focusing on the role of metacognition, because awareness domains proved to be associated with specific factors assessed by the DRS. Thus, the MISAware sub-scales "*Attention*", "*Initiation*" and "*Conceptualization*" mainly involving executive functioning were associated with the FAB which also relates to executive functions. The MISAware "*Memory*" sub-scale was associated with the FCRT assessing episodic memory. Finally, the MISAware "*Construction*" sub-scale relating to the visuo-spatial domain failed to show any significant association, perhaps because we did not introduce a visuo-spatial test in the logistic model. The referential based on a human rating yields results congruent with the conceptualization of awareness proposed by Marková [5], in its narrower form ("*insight into dementia*"). This author considers this narrower form as determined only by the patient's perception of impairment. Therefore, insight into dementia is unidimensional, so that the only dimension of awareness is that of the impairment itself, whatever the domain concerned.

Depression scores correlated only with self-reports, which could be understood as an underestimation of their abilities by patients with greater depression. This interpretation is congruent with research reporting that depression, anxiety, and certain personality traits influence subjective cognitive complaints [25]. Autonomy and apathy scored by relative and clinician correlated with relative reports. Autonomy and apathy scored by a relative lacked relevance because the person scoring was also the one who scored in the relative awareness

report. However, the correlation between relative reports and apathy scored by the clinician was more relevant. Various studies have reported associations between poorer awareness and greater apathy [1, 9, 26]. There is a growing body of evidence that apathy and impaired awareness are common manifestations in AD. Clinically, Starkstein et al. [26] reported that anosognosia predicts apathy in AD. From a neuro-anatomical viewpoint, both apathy and impaired awareness involve the anterior cingulate cortex [26], although it has been reported that awareness deficit, but not apathy, correlates with atrophy in the dorsal anterior cingulate cortex [27]. Finally, apathy is consensually divided into three dimensions: loss of interest, loss of initiative and affective blunting [28], which could influence relative ratings and clinical ratings alike, explaining why apathy was also associated with the SCSAD in the different logistic models. Apathy scored by the clinician was also correlated with patient predictions using the MISAware. This could explain the associations between the apathy scores and the total MISAware score, because an overestimation of abilities could be associated with apathy. Indeed, an apathetic patient would have a lack of sensitivity towards his deficits and inabilities. Finally, one possible relevant question is whether impaired awareness is a main component of apathy.

Several limitations should be underlined concerning this research. The sample size could be criticised given 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. Some sub-scales in awareness scales such as the SCSAD include a few items yielding unsustainable results. In addition, several models used for the awareness sub-scales did not previously suit linear modelling, requiring logistic models, leading to a loss of information probably explaining the slight differences between linear and logistic models for the global scales (see 3.1). This is why we kept exactly the same patient data as that used in our previous study [1], to confirm the same overall associations,

and to test the impact of these associations across the different domains of awareness assessed. Nevertheless, we did not anticipate at the time of our previous study [1] that we would need to explore the role of awareness dimensions. Therefore, in the present study, some scales exploring behavioural disturbances, such as the *NeuroPsychiatric Inventory* [29], which could be associated with awareness in this domain, are lacking.

In conclusion, it appears that the role of awareness dimensions varies with the method used. The *patient-caregiver discrepancy* and *clinical rating* methods do not evidence the role of awareness dimensions, while they are supposed to be focused on them [8]. In contrast, in the *prediction-performance discrepancy* method, awareness appears strongly associated with the domains assessed (as specific factors). Consequently, this method seems to be the most relevant to assess awareness dimensions in clinical practice. Nevertheless, these basic approaches are either too restricted to depression and apathy or mainly dependent on the domains assessed to obtain a broad understanding of awareness experienced by patients with AD in daily living. Thus, a phenomenological perspective proposing a person-centred approach would be more relevant to capture broader phenomena of awareness in AD [7-8].

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Table 1: Demographic, cognitive, behavioural and awareness patient data.

	Variables (lowest – best scores)[1]	**Patients** (n=61) Mean (± σ)
Demographic	Age (years)	81.26 (± 6.32)
	Education (years)	9.84 (±2.69)
	Gender (% female)	50.82
Cognitive	IADL (0 – 8)	5.97 (± 1.49)
	MMSE (0 – 30)	22.9 (± 3.62)
	BREF (0 – 18)	13.54 (± 2.78)
Behavioral / mood	GDS (0 – 15)	4.05 (± 2.42)
	AES relative (72 – 0)	46.08 (± 10.01)
	AES clinician (72 – 0)	49.43 (± 6.84)
Awareness	PCRS (-130 – 130)	-11.44 (± 19.61)
	AQ-D (90 – -90)	5.59 (± 13.05)
	MISAware (103 – 0)	8.61 (± 13.32)
	Self Consciousness (0 – 28)	23.25 (± 1.96)

[1] Lowest score indicates lowest cognitive performances, lowest level of depression, lowest level of apathy and lowest level of awareness (most impaired awareness).

AES: Apathy Evaluation Scale (scored by a relative or the clinician); **A-QD**: Anosognosia Questionnaire for Dementia; **FAB**: Frontal Assessment Battery; **GDS**: Geriatric Depression Scale; **MISAware**: Multidimensional Isomorphic Simple Awareness Assessment; **MMSE**: Mini Mental State Evaluation; **PCRS**: Patient Competency Rating Scale; **Self Consciousness**: Self-Consciousness scale in Alzheimer's disease.

Table 2: Associated factors with awareness scales and sub-scales

	Awareness scales / sub-scales	GDS	$AES_{Relative}$	$AES_{Clinician}$	Others
Referential based on human rating	**Total PCRS**	OR=0.52, *p*=0.002	OR=0.89, *p*=0.005		**MMSE** (*p*=0.004)
	PCRS Activity of Daily Living	OR=0.59, *p*=0.010	OR=0.87, *p*=0.001		
	PCRS Cognition	OR=0.57, *p*=0.003		OR=0.87, *p*=0.010	
	PCRS Int. Relations		OR=0.90, *p*=0.005		
	PCRS Emotion		OR=0.90, *p*=0.002		
	Total A-QD	OR=0.57, *p*=0.006	OR=0.87, *p*=0.003		
	A-QD Cognition	OR=0.60, *p*=0.011	OR=0.88, *p*=0.003		
	A-QD Behav. Disturb.	OR=0.76, *p*=0.059	OR=0.94, *p*=0.066		
	Total SCSAD		OR=0.89, *p*=0.019	OR=0.87, *p*=0.050	
	SCSAD Cog. Disturb	OR=0.74, *p*=0.047	OR=0.94, *p*=0.049		
	SCSAD Introspection			OR=0.84, *p*=0.007	**Education** (*p*=0.008)
	SCSAD Moral Judgments			OR=0.82, *p*=0.004	**Age** (*p*=0.023)

	Awareness scales / sub-scales	MMSE	$AES_{Relative}$	FAB	Others
Ref. based on test rating	**Total MISAware**	OR=0.68 *p*=0.002	OR=0.84, *p*=0.003		**Gender** ♀ (*p*=0.038)
	Attention			OR=0.52, *p*=0.013	**Age** (*p*=0.005)
	Initiation			OR=0.63, *p*=0.006	
	Concept			OR=0.74, *p*=0.038	
	Construction				
	Memory				

AES: Apathy Evaluation Scale (scored by a relative or the clinician); **A-QD**: Anosognosia Questionnaire for Dementia; **FAB**: Frontal Assessment Battery; **GDS**: Geriatric Depression Scale; **MISAware**: Multidimensional Isomorphic Simple Awareness Assessment; **MMSE**: Mini Mental State Evaluation; **PCRS**: Patient Competency Rating Scale; **SCSAD**: Self-Consciousness scale in Alzheimer's disease.

Table 3: Correlations across demographic, cognitive (including autonomy), behavioural (including mood) variables, self/relative awareness reports and predictions

	MMSE	$IADL_a$	GDS	$AES_{Relative}$	$AES_{Clinician}$
PCRS patient rating	ρ=-0.03, *p*=0.79	ρ=0.15, *p*=0.25	**ρ=-0.58, *p*<0.0001**	ρ=0.06, *p*=0.64	ρ=-0.01, *p*=0.92
PCRS relative rating	ρ=0.09, *p*=0.47	**ρ=0.46, *p*=0.0002**	ρ=0.04, *p*=0.77	**ρ=0.61, *p*<0.0001**	**ρ=0.33, *p*=0.0099**
A-QD patient rating	ρ=0.12, *p*=0.37	ρ=0.00, *p*=0.99	**ρ=0.45, *p*=0.0003**	ρ=0.10, *p*=0.44	ρ=0.03, *p*=0.85
A-QD relative rating	ρ=-0.26, *p*=0.04	**ρ=-0.41, *p*=0.0010**	ρ=0.10, *p*=0.45	**ρ=-0.66, *p*<0.0001**	**ρ=-0.33, *p*=0.0087**
MISAware predictions	**ρ=0.46, *p*=0.0002**	ρ=0.27, *p*=0.03	ρ=-0.08, *p*=0.55	ρ=0.22, *p*=0.09	**ρ=0.35, *p*=0.0062**

ρ: Non-parametric Spearman's correlation; $_a$: Scored by relative; **Significant correlations (*p*<0.01)**