Heterogeneity of anosognosia in Alzheimer's disease according to the object of awareness

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Abstract

Anosognosia or unawareness of neuropsychological deficits, other symptoms or the illness itself is frequent in Alzheimer's disease (AD). The aim of this study was to explore the multidimensionality of awareness in AD, comparing directly the awareness of patients in relation to several different objects: executive functions, depression, apathy, disinhibition and overall condition. Awareness was determined by discrepancy between patient- and informant-report. The results showed that the level of awareness differs according to the object studied, with awareness for overall condition and executive functions being more impaired, and relative more preservation of awareness for disinhibition and apathy. Correlational analysis suggested that awareness for executive function impairment, apathy and condition correlate strongly, while awareness of depression appears to be an independent construct. These findings have several clinical implications, highlighting the importance of a more thorough evaluation of the patients' awareness.

Keywords: anosognosia; awareness; Alzheimer's disease; cognition; ADL; behavioral disturbance

1 – Introduction

The term anosognosia refers to the lack of awareness about the illness itself or deficits, including motor, sensory, behavioural and cognitive alterations. It has been used in the context of neurological conditions such as stroke, hemiplegia and dementia (Mograbi & Morris, 2018). Indeed, recent studies showed that anosognosia is a common characteristic of Alzheimer's disease (AD) (Morris & Mograbi, 2013). Here, it has important clinical implications because of the impact on treatment compliance (Patel & Prince, 2001), the capacity to deal appropriately with potential risk situations (Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007) and its contribution to caregiver burden (Seltzer, Vasterling, Yoder, & Thompson, 1997).

There is variability in the presentation and severity of anosognosia in patients with AD, with unawareness ranging from slight minimization to complete denial of problems (Clare, Marková, Verhey, & Kenny, 2005). In addition, the reported prevalence of anosognosia in AD varies widely, depending on the study and recruitment setting (Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Mograbi et al., 2012; Sousa et al., 2015). One possible explanation for this variability, both in terms of severity and prevalence, may be the fact that awareness is a multidimensional phenomenon (Clare et al., 2011). Indeed, as highlighted by studies with different neurologic populations (e.g., cerebrovascular accident, Huntington's disease, AD), patients may have anosognosia for some deficits but preserved awareness of other difficulties (Hoth et al., 2007; Kotler-Cope & Camp, 1995; Young, de Haan, & Newcombe, 1990). This has led to the notion that awareness cannot be considered a unitary concept, but rather a phenomenon with varied presentations depending on the specific object (e.g. deficits, activities of daily living, the illness itself; (Marková, Clare, Wang, Romero, & Kenny, 2005)).

In this regard, studies exploring anosognosia in patients with AD showed that awareness

differs according to domain assessed. Using the Cognitive Behavior Rating Scales (CBRS) self- and informant-report (Williams, 1987; Williams, Little, & Haban, 1985), Kotler-Cope and Camp (1995) suggested a difference between the ability to recognize neuropsychological deficits and behavioral and psychological symptoms in people with AD. They demonstrated a significant discrepancy between ratings by patients and informants only for the five cognitive scales: language disorder, higher cognitive deficits, memory disorder, dementia, apraxia. For the four scales evaluating the behavioral deficits (agitation, need for routine, depression, disorientation), the difference was not statistically significant. Vasterling et al. (1995) published similar results also pointing that patients with AD present better awareness of behavioral difficulties relative to cognition. Nevertheless, Verhülsdonk et al. (2013) highlighted in a recent study that patients with AD demonstrate difficulty recognizing their own depressive symptoms, leading them to propose the term "affective anosognosia."

Further support for the multidimensional nature of anosognosia in AD is given by evidence that the correlation of anosognosia with neuropsychiatric symptoms also differs according to the domain of awareness assessed (for review, Starkstein, 2014). Starkstein et al. (1996) indicated that awareness of cognitive difficulties is associated with depression, while awareness of behavioral problems is correlated with disinhibition. More recently, Spalletta et al. (2012) found a correlation between awareness of behavioral deficits and apathy.

In support of these findings, Starkstein et al. (1996) proposed, based on a factor analysis of the Anosognosia Questionnaire-Dementia (AQ-D) (Migliorelli et al., 1995), a division of the concept of anosognosia into two domains: lack of cognitive awareness and lack of behavioral awareness. More recently, they extended these findings by analysing four domains of anosognosia in a larger series of patients with AD (n=750), including

awareness for basic activities of daily living, for instrumental activities of daily living, for depression and for disinhibited behaviors (Starkstein, Jorge, Mizrahi, & Robinson, 2006). Analysing another instrument evaluating awareness in dementia, the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD) (Dourado, Marinho, Soares, Engelhardt, & Laks, 2007), Dourado et al. (2014) presented also a four-factor division: awareness for activities of daily living, awareness of cognitive functioning and health condition, awareness of emotional state, and awareness of social functioning and relationships.

In summary, there are three types of argument supporting the idea of anosognosia as a multifaceted phenomenon: firstly, studies highlighting that patients with AD show varying degrees of awareness in relation to different 'objects' of awareness (Kotler-Cope & Camp, 1995; Vasterling et al., 1995; Verhülsdonk et al., 2013); secondly, correlational analysis indicating differences in the relation between anosognosia and neuropsychiatric symptoms according to the nature of deficits evaluated (Spalletta et al., 2012; Starkstein et al., 1996); and finally, factorial analysis showing that instruments measuring unawareness can be divided into various factors (Dourado et al., 2014; Starkstein et al., 2006; Starkstein et al., 1996).

Despite the growing understanding of the complexity of awareness, to the best of our knowledge no study has been published comparing directly awareness for cognitive deficits, behavioral problems and mood disorder. The purpose of the present study is to focus on the heterogeneity of anosognosia in AD patients according to the object, comparing directly awareness for five factors: executive functioning, depression, apathy, disinhibition and the condition itself. Considering the findings from prior studies, we hypothesized that the patients' awareness would differ according to the different domains evaluated.

2 – Methods

2.1. Participants

Twenty participants with mild to moderate AD were included in the study, recruited either from the South London and Maudsley / Institute of Psychiatry Biomedical Research Centre (BRC) Dementia Case Register or from the St George's Healthcare NHS Trust (London) Dementia clinic. Diagnosis was made using DSM-IV criteria for Dementia of the Alzheimer's type (American Psychiatric Association, 2000), with Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975)) scores of 18 or above (Mungas, 1991; NICE, 2006), in order to focus the present study on mild to moderate dementia. Consecutive patients who fulfilled the study eligibility criteria were approached.

Exclusion criteria were history of neurological disorder (other neurological disorder than AD, also excluding cases with mixed AD and vascular dementia); history of head injury resulting in loss of consciousness for more than an hour; history of alcohol or substance abuse (based on ICD-10 criteria); and history of diagnosed major psychiatric illness or current psychological comorbidity (for example, mood disorder).

2.3. Measures

2.3.1. Frontal Systems Behavior Scale (FrsBe)

The FrSBe (Grace & Malloy, 2001), formerly Frontal Lobe Personality Scale (FLoPS), was designed to measure behavioral impairment in various neurologic populations including people with dementia (e.g. AD, dementia in Parkinson's disease, and vascular

dementia), stroke and head injury (Malloy & Grace, 2005). The 46-item scale evaluates three components: executive dysfunction, disinhibition and apathy. Every item is rated on a 5-point Likert scale and higher ratings correspond to greater abnormal behavior. In order to assess awareness of cognitive/behavioral deficits, self and informant versions were used.

2.3.2 Geriatric Depression Scale (GDS)

Depression was assessed using the GDS 15-item scale, which was developed to evaluate depressive symptoms specifically in older adults (Sheikh & Yesavage, 1986). This short version of the questionnaire consists of 15 items (range 0–15 points), with higher scores indicating more-severe depressive symptoms. In order to measure awareness regarding depressive symptoms, self and informant versions were used.

2.3.3. Anosognosia questionnaire

As an assessment for broader awareness into their condition, AD patients were examined with the Anosognosia Questionnaire-Dementia (AQ-D; (Migliorelli et al., 1995)). The AQ-D was specifically designed to measure anosognosia in dementia, covering functional changes commonly found during the course of this illness. The AQ-D is a 30-item questionnaire with patient and informant version, divided into two sections; the first section assesses performance of basic and instrumental activities of daily living, whereas the second section examines changes in mood and behavior in relation to daily activities. Scoring for each item ranges from 0 (never experiences impairment in the activity) to 3 (always experience impairments), with anosognosia determined by calculating discrepancies between patient and informant report.

2.3.4. Background variables

Participants were assessed on the revised Addenbrooke's Cognitive Examination (ACE-R; (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006)). The ACE-R covers a wider range of cognitive functions, being divided into five domains: attention and orientation, memory, verbal fluency, language and visuospatial skills. Higher scores indicate better cognitive ability and the maximum total score is 100 (min=0).

In addition to the ACE-R subscale, memory was tested using the word list memory task from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) battery (Morris et al., 1989). A ten-item word list is presented to the participant over three trials, each trial immediately followed by a recall phase (immediate recall score; min–max: 0–30). After a short delay (approximately five minutes), the participant is asked to recall as many of the 10 words as they can (delayed recall score; min–max: 0–10). Finally, immediately after the Delayed Recall task, a list of twenty words, with ten new words and ten from the previous list, is shown to participants. The participants respond by identifying (forced choice yes-no) which words had been presented before (recognition score; min–max: 0–20).

To screen for levels of depression and apathy clinically, clinician ratings were used. For depression the selected assessment was the Cornell Scale for Depression in Dementia (clinician; (Alexopoulos, Abrams, Young, & Shamoian, 1988)). The Cornell is a 19-item clinician administered interview that relies on information from both the patient and an informant. Each item represents a common symptom of depression in older adults and is scored as absent (0), mild (1) or severe (2). Total scale scores vary from 0 to 38, with higher scores indicating greater severity of depression. Apathy was measured using the clinician version of the Apathy Evaluation Scale (AES; (Marin, Biedrzycki, &

Firinciogullari, 1991)). The AES-clinician is a semi-structured interview about the participant's interests and daily activities. In the current study, information from the interview was confirmed with an informant in the case of the patients. It is scored in an 18-item scale with a Likert-like system (1 to 4 for each item), with some items being reverse scored; scores range from 18 to 72 and higher scores mean more apathy.

2.4. Ethical issues

All participants provided informed consent, with caregivers also giving their agreement for the patient to take part. The project was approved by the South London and Maudsley/ Institute of Psychiatry Ethics Committee (Research Ethics Committee number 08/H0807/6).

2.5. Statistical analysis

For each measure (FrsBe subscales [apathy, disinhibition and executive functions], GDS and AQ-D), corrected discrepancy ratio scores (Clare, Whitaker, & Nelis, 2010) were calculated using the following formula: e.g. for the FrsBe, (FrsBe-Self - FrsBe-Informant/((FrsBe-Self + FrsBe-Informant)/2)). This method was applied in order to control scaling effects relating to between-subject differences in level of rating or performance. It also provides direct comparison of awareness of domains measured with questionnaires with varying number of items. Corrected discrepancy scores close to zero indicate good agreement participant-informant. Positive scores suggest that participants underestimate their abilities and negative scores suggest that self-rating of difficulties is lower than informant rating (overestimation of ability).

A repeated-measures ANOVA was used to compare the discrepancy ratios across five domains: condition (AQ-D), cognitive ability (FrsBe executive functions), depression (GDS), apathy (FrsBe apathy subscale) disinhibition (FrsBe disinhibition subscale). Pairwise comparisons with post-hoc t-tests followed the ANOVA. To avoid inflation of type I error, comparisons were adjusted with Bonferroni-Hochberg corrections.

Pearsons correlations investigated the relationship between different forms of awareness. To explore associations of awareness according to object, Pearson correlations were calculated between each awareness score and demographic (age, gender and educational level) and clinical variables (clinician ratings of apathy and depression, cognitive level [total score in the ACE-R] and memory [total immediate recall]). In the case of gender, point-biserial correlations were used. Considering the exploratory nature of this analysis, corrections for familywise error rate were deemed unnecessary.

3 – Results

3.1. Sample characteristics

Socio-demographic and clinical characteristics of the sample can be seen in Table 1. Regarding the level of anosognosia of the sample, an unpaired t-test showed that the mean AQ-D score was within the range of, and not significantly different from, the values reported in other studies using the same measure (Migliorelli et al., 1995; Starkstein et al., 1996) (respectively, $t(121) = 1.35$, $p = .18$; $t(188)= 1.02$, $p = .31$).

PLEASE INSERT TABLE 1 HERE

3.2. Awareness of symptom or condition

The repeated-measures ANOVA indicated significant differences between awareness types ($F (4, 76) = 15.47$, $p < .001$, $\eta_p^2 = .45$). Pairwise comparisons suggested that awareness of condition is significantly more impaired than all other forms of awareness ($p < .001$), with the exception of awareness of mood disorder ($p = .096$). Awareness of executive functions was also significantly worse than awareness of disinhibition ($p = .017$) and of apathy ($p = .024$). There were no other significant differences. Results can be seen in Figure 1.

PLEASE INSERT FIGURE 1 HERE

3.3. Correlational analysis

Correlations between awareness scores can be seen in Table 2. The majority of awareness scores showed positive correlations, with the coefficients varying from strong significant correlations (e.g. awareness of executive functions and awareness of apathy [$r = .88$, $p < .001$] or awareness of condition [$r = .89$, $p < .001$]) to weaker correlations (e.g. awareness of disinhibition and awareness of condition [$r = .46$, $p < .05$] or awareness of apathy [$r = .53$, $p < .05$]), with two non-significant correlation coefficients (awareness of depression and awareness of disinhibition [$r = .25$, $p = .283$] and awareness of depression and awareness of condition [$r = .03$, $p = .902$]).

PLEASE INSERT TABLE 2 HERE

There were no significant associations between types of awareness and educational level, gender, age, memory, cognitive level or apathy. There was a significant positive correlation between awareness of condition and depression (r = .50, p = .025) and a trend for a positive correlation between depression and awareness of executive functions (r = .43, p = .058).

4 – Discussion

The results showed, in a typical AD sample, that the level of awareness differs according to the object studied. Using a ratio method, which allowed direct comparison of unawareness as measured by different scales and controlled between-subject variation due to level of rating or performance, unawareness was shown to be higher for overall condition and executive functions, with relatively more preserved awareness for disinhibition and apathy. Correlational analysis suggested the existence of an association between awareness of condition and awareness for other objects, with the exception of depression. Awareness of depressive symptoms was not related to awareness of condition, nor of disinhibition, and the correlation with awareness of executive functions and apathy was weak.

Awareness was lower for condition, activities of daily living and consequences of the illness, which characterises unawareness in AD as a form of anosognosia, considering the etymology of the term (a – noso – gnosia; unawareness of illness). This highlights the important clinical impact of unawareness in AD, suggesting why it is linked to exposure to risks and treatment compliance (Patel & Prince, 2001; Starkstein et al., 2007). Unawareness of executive functions was also higher than for other objects, and this may

be linked to difficulties in goal-directed activities, leading to unawareness of instrumental activities of daily living, and loss of autonomy and quality of life.

Of note, the results showed better awareness for apathy and disinhibition than for executive functions. The role of the frontal lobes in awareness has been discussed (Harwood et al., 2005; Salmon et al., 2006), but the current results suggest that the nature of the frontal function may also be relevant when determining awareness. Alternatively, even though executive functions rely on the frontal lobes, the role of other brain areas has been emphasised (Collette et al., 2005; Robinson, Calamia, Gläscher, Bruss, & Tranel, 2014), while apathy and disinhibition may be more strictly linked to frontal lobe dysfunction. The better awareness for a cognitive frontal symptom than for behavioral frontal symptoms can be linked to results highlighting that, generally, unawareness of cognitive deficits is greater that of behavioral disturbance (Kotler-Cope & Camp, 1995; Vasterling et al., 1995).

The results suggest that awareness for executive functions, apathy and condition correlate strongly, while it seems that awareness of depression is a different construct. With this respect, previous studies have emphasised how awareness of emotional state differs from awareness for activities of daily living and for cognitive functioning (Dourado et al., 2014; Nelis et al., 2011). The results of the present study are in line with findings from Verhülsdonk et al. (2013), who highlighted a lack of relationship between anosognosia (awareness of condition) and awareness of depressive symptoms.

Most studies exploring the relationship between depression and anosognosia in AD suggest a link between these variables, with greater awareness associated with more depressive symptoms (e.g Clare et al., 2011; Harwood, Sultzer, & Wheatley, 2000; Mograbi & Morris, 2014). The current study provides further evidence for this, with awareness for condition and executive functions showing moderate positive correlations

with depression. This relationship was not observed in the case of behavioral and mood disturbance variables, such as apathy, depression and disinhibition. This suggests that depression impacts differentially on awareness according to the object and also contributes to the discussion regarding the direction of causality between depression and awareness (Mograbi & Morris, 2014). It has been proposed that depression leads to more awareness because of general over-reporting of problems or depressive realism, but the current findings do not support this view, since some forms of awareness did not correlate with depression. A more plausible explanation, in the context of current findings, is that awareness leads to more depressive symptoms, with awareness of condition and executive functions contributing more to depression arguably because of a greater impact in everyday life.

A control group was not used in the comparison of awareness concerning different objects, because, by definition, a healthy control group would not show the cognitive impairments or behavioral disturbance associated with dementia. Also regarding the awareness measure used in the present study, it is important to note that a discrepancy between caregivers and patients reports does not mean necessarily that there is a deficit in the specific domains. However, in the literature, patient-carer discrepancy is a widely used method to assess awareness (Clare et al., 2005). Another limitation of the study refers to the small sample size, which may affect generalizability and statistical power. Regarding generalizability, the sample is similar to other studies exploring awareness in AD and typical of patients in the mild to moderate range of the illness. In addition, the study found a number of significant results, and where significant differences were not found, effect sizes were typically small (e.g. some of the correlations).

In summary, the results of the present study underline the complexity of anosognosia and the relative independence of awareness for depressive symptoms in relation to other

objects. In terms of clinical implications, the study suggests that awareness affects differentially behavioral and cognitive symptoms, indicating the importance of a more extensive evaluation of the patients' capacity to appreciate the presence of deficits and symptoms. Despite having low correlations with other awareness scores, unawareness for depressive symptoms was found to be high. This has important clinical implications in terms of depression diagnosis in the context of dementia. It suggests, for instance, that if diagnosis is based on patients' report, depressive symptoms can be underestimated and the condition remain untreated. Future studies should explore further the correlations between awareness for different objects and implications for quality of life of patients and caregivers.

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Table 1 – Background variables

Variable	AD group (n=20) Mean (SD)
Age	80.2 (6.7)
Gender*	12 / 8
Years of education	10.6 (2.4)
CERAD Immediate recall	12 (3.9)
Delayed recall	1.3 (1.2)
Recognition	15.2 (3.6)
# of Intrusions	2.0 (1.7)
ACE-R Total	64.1 (10)
Attention and	14.2 (2.3)
orientation Memory	9.4 (4.1)
Fluency	7.2 (3.0)
Language	20.2 (3.4)
Visuospatial	
MMSE	23.3 (2.9)
AES	40.9 (9.2)
CORNEL	4.0 (3.7)
AQ-D	20.3 (12.1)

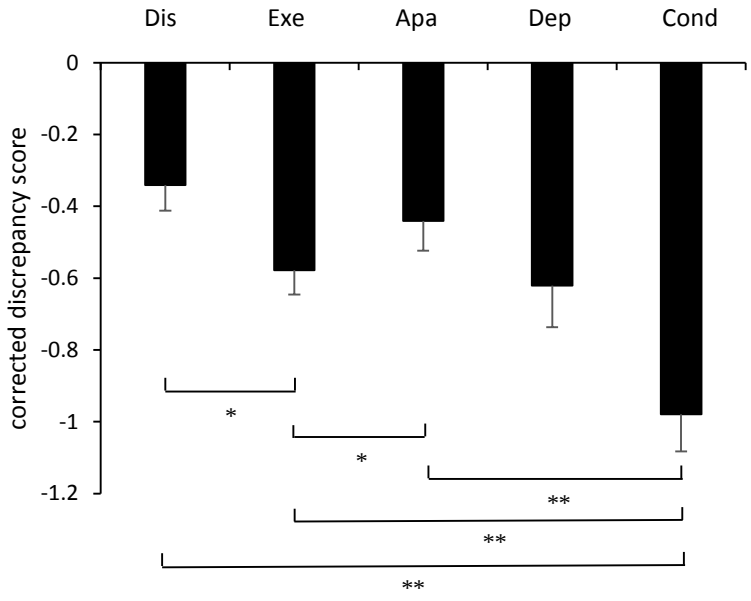
* # female/ male.

Table 2 – Correlations between awareness variables

Variable	Disinhibition	Executive functions	Apathy	Depression
Executive functions	**.56**			
Apathy	**.53**	**.88**		
Depression	.25	**.52**	**.52**	
Condition	**.46**	**.89**	**.83**	.03

Significant results are presented in bold.

Figure 1 – Discrepancy ratios for different domains of awareness



Dis – Disinhibition; Exe – Executive functioning; Apa – Apathy; Dep – Depression; Cond – Condition; * $p < .05$; ** $p < .001$