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Research Article

Predictors of cognitive anosognosia in older adults with suspected dementia

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ABSTRACT

Objective: Anosognosia heterogeneously affects cognitive functioning and indeed, at the very onset of dementia symptoms. This raises the question of accountable predictors of each cognitive impairment. The objective of this study was to identify the cognitive and non-cognitive predictors of so-called cognitive anosognosia.

Method: A paradigm based on the discrepancies between performance predictions and actual performance in the light of the Dementia Rating Scale (DRS) helped distinguish cognitive anosognosia in relation to four major functions: Attention Initiation-perseveration, Conceptualisation and Memory. Patients achieved a complete set of neuropsychological tests and assessments of the level of anxiety, apathy and functional independence.

Results: Significant correlations existed between all cognitive anosognosia scores (AS) and neuropsychological performance scores of the participants. Similarly, significant correlations were found between the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores and the Initiation and Conceptualisation AS and between anxiety score and Conceptualisation and Memory AS. However, the regression models were exclusively cognitive for Attention Initiation-perseveration and Memory AS. Only the Conceptualisation AS was predicted by a non-strictly cognitive regression model including the ADL score.

Conclusions: If the different specific cognitive anosognosias are predicted by separate sets of variables, our results emphasise that dysexecutive impairment plays a major role regardless of the deficiencies considered.

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Introduction

Public significance statements: The predictors of anosognosia are primarily cognitive. The predictors vary depending on the “object” of awareness. The affects do not have any impact on cognitive anosognosia. Executive impairment is the main predictor of cognitive anosognosia.

Cognitive disorders occur with advancing age, and anosognosia is a condition that can compromise diagnoses and/or acceptance of support. Anosognosia is defined as the alteration of “the reasonable or realistic perception or appraisal of a given aspect of one’s situation, functioning or performance, or of the resulting implications” [1].

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During the prodromal stage, upon suspicion of cognitive impairment, despite a lower intensity and frequency than in the diagnosed diseases, anosognosia is already a factor associated with poor prognosis [2-4].

This symptom is considered a direct consequence of the disease and heterogeneously affects cognitive functions, such as hardly affecting memory processes at the onset of the disease and visuo-constructive abilities or executive functions at a later stage [5-8].

This heterogeneity in the objects of awareness raises the question of identifying the general or specific anosognosia predictors for each cognitive impairment [9]. In dementia, the first hypotheses explored the involvement of memory disorders while many current studies report correlations between anosognosia and neuropsychological processes such as executive processes, in particular [10-14].

The *Cognitive Awareness Model* provides an understanding of anosognosia as resulting from a deficiency in the modules that, under executive control, regulate our behaviors and recognize mistakes via comparators, which compare current performance with prior experiences (stored in a *Personal DataBase*) [15]. In anosognosia, information updates are no longer assured, errors are no longer taken into account, and behavior is therefore not adjusted to match current performance. According to the modules involved, deficiencies involve separate initial disorders and various expressions of anosognosia [5, 15].

Research on predictors of awareness of cognitive deficiencies –cognitive anosognosia –faces several challenges at the moment of the suspicion of dementia disorder.

Most researches measure generally little awareness of cognitive disorders (e.g., the functional intelligence score of the Anosognosia Questionnaire for Dementia (AQ-D) [16, 17]. In line with the CAM model, we should study the diversity of cognitive processes globally or specifically involved in the awareness of various cognitive deficiencies.

In addition, other non-cognitive clinical factors can contribute to the awareness of disorders and of behavioral disorders in particular, including apathy anxiety, and difficulties in daily life activities [18-21].

The objective of this study was to identify cognitive and non-cognitive predictors of cognitive anosognosia. We expected to find specific cognitive and non-cognitive predictors for each score measuring the awareness of disorders. This study involved patients with signs of early impairment or existing undiagnosed cognitive impairment. A paradigm based on the discrepancies between actual performance and performance predictions helps to distinguish the awareness of cognitive disorders, function by function.

Methods

Participants

Patients were recruited from a Memory Center in the Bateliers Hospital in Lille, France. The entire protocol was performed over one-half of a day, in accordance with a standard Memory Center consultation. Patients were submitted to a complete clinical and neuropsychological

evaluation, after which a probable diagnosis was made based on published criteria.

The inclusion criteria included suspicion of cognitive impairment, a *Mini-Mental State Examination* greater than or equal to 15 points and fluency in French. Another criterion was the presence of an informing caregiver from the patient's personal life, hence not a professional [22]. The participants were then asked to complete the Functional Independence questionnaires in a hetero-evaluation, as in a conventional evaluation situation. The criteria for non-inclusion included the presence of uncorrected sensory deficiencies that might prevent the realization of a classical clinical picture, the presence of a language disorder such as aphasia, or a major deficiency in the understanding and diagnosis of a psychotic table (Axis1 DSM-IV).

Consent from each patient and family caregiver was collected prior to any evaluation, in accordance with the Declaration of Helsinki.

Cognitive and psychological assessment

The MMSE and the Dementia Rating Scale were used as measures of overall cognitive functioning [22, 23]. The DRS has allowed us to characterize the five major cognitive functions: attention, initiation-perseveration, construction, conceptualization and memory.

The *memory* assessment was performed using the Buschke Selective Reminding Test (immediate recall, total free and total recall, delayed total and free recall, and recognition) [24]. *Visuospatial* abilities were evaluated by copying the figures of the Consortium to Establish a Registry for Alzheimer's Disease [25]. The tests of *executive functions* measured mental flexibility inhibition (Victoria Stroop Test (VST), perseverative errors (Buschke test, TMT B, VST uncorrected errors) and verbal initiation (literal fluency - letter P) [26-28]. Some patients did not have the ability to perform all the tests because of major cognitive disorders.

To the above assessments, we added a functional independence and affective hetero evaluation by a caregiver. *Functional independence* was assessed using the following scales: The Activities of Daily Living and Instrumental Activities of Daily Living scales [29, 30]. We investigated the *anxiety* level using the Hamilton Anxiety Depression Scale, retaining only the items concerning anxiety [31]. *Apathy* was studied through the total score of the Apathy Inventory [32].

Measurement of anosognosia

The Multidimensional Isomorphic Simple Awareness (MISA) procedure was used to assess *cognitive* anosognosia among the participants (for additional details, see Antoine et al., 2013) [6]. This tool is based on subjective self-ratings that are compared with actual objective performance on neuropsychological tests. The patients were asked to predict their DRS performance on a dichotomous scale for each of the tasks of the DRS after hearing and seeing the task and prior to actually performing the task. Each patient was required to simply predict whether he/she would perform the task (1) well or (2) incorrectly before performing each main item of the DRS. From the predictions and the real score (RS), a prediction score (PS) is calculated for each subscale. This

PS represents the quantity of correct answers that a participant believes he will obtain for each item presented. If a participant overestimates his own performance, his PS will be significantly higher than his real performance (i.e., the RS). For the anosognosia score (AS), we calculated the discrepancy between the RS and the newly calculated PS.

This procedure was applied to 4 of the 5 subscales of the DRS: attention, initiation-perseveration, conceptualization and memory. The construction subscale was not included because of the small number of items in that subscale, which would not allow a reliable comparison with other subscales.

Design of the scores

The DRS exhibits an inconvenience in its subscales in that the total scores differ, which makes their comparison awkward when added together. To provide each subscale the same importance in the DRS overall score, we used the weighted mean for the RS rather than for the PS. Thus, we corrected each subscale score by their respective number of items and converted it into a percentage to facilitate readability. For example, the total score for the attention subscale was divided by 37, which corresponds to the maximum score for this subscale and then multiplied by 100 to obtain a percentage. Finally, all the corrected subscale scores were averaged to obtain the weighted mean for the overall DRS score for the RS and the PS. All analyses were conducted with all scores in terms of the percentage of good answers.

Statistical analyses

We used a Pearson's correlation coefficient to observe the links between the scores of anosognosia (AS) by category and the results for different neuropsychological tests. We conducted bivariate and multiple *stepwise* regression analysis on the specific AS to highlight the neuropsychological predictors for each category. Each variable was

Table 2: Correlations between DRS-specific ASs (Attention, Initiation-Perseveration, Conceptualization, and Memory) with neuropsychological tests and affective and functional independence questionnaires

Correlations between specific ASs and neuropsychological and functional data				
	Attention AS	Initiation AS	Concept AS	Memory AS
Buschke test				
Immediate recall	-	-0.35**	-0.27*	-0.48***
Total free recall	-	-0.40***	-	-0.26*
Total total recall	-	-0.36**	-	-
Delayed free recall	-	-0.36**	-	-
Delayed total recall	-	-0.38**	-	-
Recognition	-	-0.28*	-	-0.36**
Intrusions	-	-	-	-
Perseverative errors	-	-	0.50***	0.58***
CERAD figures	-	-0.32**	0.39***	0.24*
Trail Making Test Reaction time	0.32*	-	-	-
Trail Making Test Perseverative errors	0.46**	-	-	-
Victoria Stroop Test Reaction time	-	-	-	-
Victoria Stroop Test Inhibition errors	0.33**	0.49***	0.42***	-
"P" Alphabetic fluency	0.32**	0.45***	0.42***	-
Total ADL	-	-0.43***	-0.43***	-
Total IADL	-	-0.34**	-0.31**	-
HADS – Anxiety	-	-	0.25*	0.24*
Total IA	-	-	-	-

included for a probability of less than 0.01 and excluded for a probability greater than 0.05. The final regression model chosen corresponds to the significant model with the highest adjusted R².

Results

Seventy-six patients met the set of criteria and therefore exhibited a suspicion of cognitive disorders. Their demographic and clinical data are summarized in Table 1.

Table 1: Patients' clinical and demographic data

Gender (women, %)	71.05%	
Age (±SD)	82.4 (6.1)	
MMSE	23.8 (3.5)	
DRS Total RS weighted mean	84.7 (9.5)	
DRS Total AS weighted mean	8.2 (6.3)	
Attention AS	n=76	5.9 (4.7)
Initiation AS	n=76	8.5 (10.0)
Conceptualization AS	n=76	5.2 (7.2)
Memory AS	n=76	15.4 (14.6)

Note. MMSE, Mini Mental Test Examination; DRS, Dementia Rating Scale; RS, Real Score; AS, Anosognosia Score.

Correlations

A bivariate correlation matrix is presented in Table 2 and was performed using 4 cognitive ASs (attention, initiation-perseveration, conceptualization, memory) and neuropsychological, affective and functional independence variables.

Note. DRS, Dementia Rating Scale; AS, Anosognosia Score. ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; IA, Apathy Inventory; Pearson's correlation coefficient; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The AS of the attention subscale was positively correlated with 3 tests: TMT (reaction time: $r = 0.32$, $p < 0.05$, PE: $r = 0.46$, $p < 0.01$), VST (IE: $r = 0.33$, $p < 0.01$) and alphabetical fluency ($r = 0.32$, $p < 0.01$). However, attention AS was not correlated with the total score of the HADS ($r = 0.07$, $p = 0.5705$), IA ($r = -0.19$, $p = 0.11$), ADL ($r = -0.15$, $p = 0.224$) or IADL ($r = -0.08$, $p = 0.498$).

Initiation AS correlated with all subscores of the Buschke test (except for PE, all $p < 0.05$), the test of the CERAD ($r = -0.32$, $p < 0.01$), VST (IE: $r = 0.49$, $p < 0.001$) and alphabetical fluency ($r = 0.45$, $p < 0.001$) as well as with the total scores of the ADL ($r = -0.43$, $p < 0.001$) and IADL ($r = -0.34$, $p < 0.01$). Initiation AS was not correlated with other measures (HADS, $r = 0.07$, $p = 0.55$; IA, $r = 0.09$, $p = 0.47$).

Conceptualization AS showed significant correlations with the Buschke test (ImmR: $r = -0.27$, $p < 0.05$; PE: $r = 0.50$, $p < 0.001$), the test of the CERAD ($r = 0.39$, $p < 0.001$), the VST (IE: $r = 0.42$, $p < 0.001$) and alphabetical fluency ($r = 0.42$, $p < 0.001$) as well as with the total scores of the HADS ($r = 0.25$, $p < 0.05$), ADL ($r = -0.43$, $p < 0.001$) and IADL ($r = -0.31$, $p < 0.01$). Only the IA was not correlated ($r = 0.06$, $p = 0.65$).

Finally, Memory AS was significantly correlated to the Buschke test (ImmR: $r = -0.48$, $p < 0.001$; Total free recall: $r = -0.26$, $p < 0.05$; Recognition: $r = -0.36$, $p < 0.01$; PE: $r = 0.58$, $p < 0.001$) and with the test of the figures of the CERAD ($r = 0.24$, $p < 0.05$), as well as with the HADS anxiety score ($r = 0.2425$, $p < 0.05$). Memory AS was not correlated with the total scores in the IA ($r = 0.01$, $p = 0.94$), ADL ($r = -0.11$, $p = 0.389$) and IADL ($r = -0.12$, $p = 0.343$).

Stepwise regression analyses

Regression analyses following the stepwise method were used to determine the links between AS (a single dependent variable) and cognitive, affective and independence disorders (as predictor variables). Table 3 contains each step for all 4 scores of anosognosia, and Figure 1 summarizes the significant predictive models by AS.

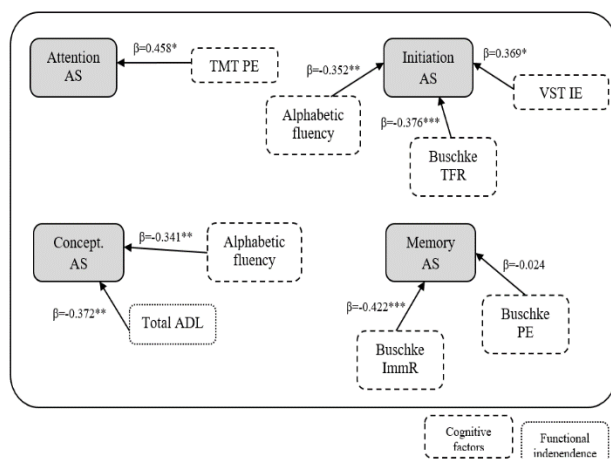


Figure 1: Modeling of specific AS predictors

Table 3: Stepwise regression analyses

Attention AS		
N=41	AR ²	β
Step 1	0.189	
TMT B-A Perseverative errors		0.458**
Initiation – Perseveration AS		
N=63	AR ²	β
Step 1	0.229	
Victoria Stroop Inhibition errors		0.492***
Step 2	0.336	
Victoria Stroop Inhibition errors		0.399**
“P” Alphabetic fluency		-0.328**
Step 3	0.490	
Victoria Stroop Inhibition errors		0.369**
“P” Alphabetic fluency		-0.352**
Total Free recall Buschke Test		-0.376***
Conceptualization AS		
N=66	AR ²	β
Step 1	0.173	
Total ADL		-0.430***
Step 2	0.278	
Total ADL		-0.372**
“P” Alphabetic fluency		-0.341**
Memory AS		
N=69	AR ²	β
Step 1	0.332	
Buschke Perseverative errors		-0.014
Step 2	0.323	
Buschke Perseverative errors		-0.024
Recognition Buschke Test		-0.422***

Note. AS, Anosognosia Score. AR², Adjusted R²; TMT, Trail Making Test; ADL, Activities of Daily Living; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Only the attention AS was predicted by a single variable: TMT PE ($F = 10.33$, $p < 0.01$, $R^2 = 0.189$, $\beta = 0.458$, $p < 0.01$).

The AS scores of conceptualization and memory were explained by the regression models with two variables, respectively; total ADL ($\beta = -0.37$, $p < 0.01$) – alphabetical fluency ($\beta = -0.34$, $p < 0.01$) ($F = 12.15$, $p < 0.01$, $R^2 = 0.278$) and immediate recall ($\beta = -0.42$, $p < 0.001$) – PE Buschke ($\beta = -0.02$, $p = 0.82$) ($F = 18.63$, $p < 0.001$, $R^2 = 0.323$).

The score of anosognosia on the initiation-perseveration subscale was predicted by a model with 3 predictors as follows: VSTIE ($\beta = -0.37$,

$p < 0.01$) – alphabetical fluency ($\beta = -0.35$, $p < 0.01$) – total free recall Buschke ($\beta = -0.38$, $p < 0.001$) ($F = 17.30$, $p < 0.001$, $R^2 = 0.489$).

Discussion

The objective of this study was to identify cognitive and non-cognitive predictors of anosognosia and their relation to the disturbances of different cognitive functions. We expected to find specific predictors for each awareness disorders score and to identify cognitive and non-cognitive predictors.

Neuropsychological and non-cognitive actors of cognitive anosognosia

Our results initially confirmed significant correlations between the cognitive ASs and neuropsychological performance scores of the participants. We also observed significant correlations between the loss of functional independence score and the ASs of initiation and conceptualization. An equivalent significant link was found between the anxiety score and awareness disorders in conceptualization and memory.

Clinical correlations of cognitive anosognosia are not restricted to cognitive functioning. Other dimensions of the patient's life are considered, including functional independence and its affects, which correlates with the current literature [16]. However, we did not find any significant link between cognitive anosognosia and the presence of apathy, although this result has been previously widely documented [18].

Each of the four cognitive ASs correlated significantly with a specific set of cognitive and non-cognitive variables. Therefore, it appears that cognitive anosognosia should not be considered as a whole but instead divided into "specific cognitive anosognosias" for each deficiency, i.e., specific to each "object" of awareness [9]. This design has already been noted in studies considering anosognosia as a set of heterogeneous phenomena [7, 21]. Furthermore, based on observed correlations, we have emphasized a regression model for each cognitive impairment considered.

Predictors of cognitive anosognosia

The second important result showed that the predictors of different ASs differed from one another. The various specific cognitive anosognosias are predicted by separate sets of variables, which reinforce the heterogeneous nature of anosognosia and demonstrates that each object of awareness has a different origin. Therefore, anosognosia must be assessed at a process level to better understand this phenomenon.

In addition, although the correlations showed many links between all considered clinical variables and the four scores in which anosognosia was measured, the regression models are exclusively cognitive for attention, initiation-perseveration and memory ASs. Only the conceptualization AS is predicted by a model that is not focused strictly on cognitive decline and includes the total ADL score. Furthermore, deficiencies that predict the best ASs relate either mostly to the executive processes or the memory processes. Indeed, out of seven predictors that were identified, five are related to the executive domain.

Specifically, the results show the involvement of specific executive processes that are perseverative errors and predictors of three ASs out of four. The perseverations are signs that are characteristic of executive impairment and show a deficiency in terms of monitoring and updating *online* information [33].

These results are consistent with the CAM model of Morris and Mograbi (2013) for which the comparator mechanisms are at two levels: sensory-motor and central cognitive [15]. This last level is underpinned by attentional, executive (monitoring) and mnemonic (semantic memory) networks that are typically affected by neurodegenerative diseases. Thus, the entanglement of executive disorders that prevent the updating of information and memory disorders that disrupt the encoding and retrieval form a solid basis for the emergence of anosognosia. The type of anosognosia should vary based on the disorders and therefore the cognitive modules that are affected, which our study seems to support.

Cognitive anosognosia and daily life

Our study tends to confirm that daily activities have a significant impact on anosognosia in terms of cognitive deficiencies. However, if the ADLs are negatively and significantly correlated with scores of anosognosia, then these findings only pertain to the executive scales of conceptualization and initiation-perseveration and not to those scales involving memory processes. In regression models, the ADLs are only predictors of the conceptualization AS, a scale corresponding to high level executive processes. The ADLs are known to be affected by deficiencies in executive functions, and their involvement in the perception of cognitive impairment also seems now confirmed.

This study has several limitations. Analyses were limited by the size of the total sample and by the diagnostic category in particular. It would be interesting to pursue this type of research for each type of diagnosis, such as Alzheimer's disease, MCI, and vascular and mixed dementia. Furthermore, the anosognosia assessment methodology could be improved. The methodology in this study is based on a scale screening of cognitive functions whose scores remain composite. A study involving deficiencies that were less coarse would continue the modeling work of anosognosia.

Conclusions

Despite these limitations, our results emphasize that executive dysfunction plays a major role in cognitive anosognosia and associated deficiencies in memory, attention, initiation-perseveration and conceptualization. Executive functioning involves very different processes, and the challenge is how to identify those that are more involved. In addition, some predictors are attributable to other areas, including mnemonic [16]. The multiplicity of the phenomena might suggest the involvement of additional variables not considered in our study. Future studies are required to more comprehensively identify the phenomena involved and to study their roles and relative weights in structural modeling processes of anosognosia.

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