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# Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates

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ABSTRACT

Anosognosia is present in a large proportion of patients with mild Alzheimer's disease (AD), and its frequency increases with the progression of the illness. Several instruments have been validated to assess anosognosia in AD, but there is no consensus regarding the best diagnostic strategy. Anosognosia in AD is a significant predictor of apathy and is significantly related to lower depression and anxiety scores, more severe caregiver burden and dangerous behaviours. Studies using different imaging modalities have demonstrated an association between anosognosia and dysfunction in frontal, temporomedial and temporoparietal regions. The mechanism of anosognosia remains unknown, but it has been explained as a consequence of deficits of encoding and updating biographical memory, and dysfunction of comparator, executive and metacognitive systems.



## 1. Introduction

Clare et al. (L. Clare et al., 2012c) defined awareness as "the reasonable or realistic perception or appraisal of a given aspect of one's situation, functioning or performance, or of the resulting implications, which may be expressed explicitly or implicitly." Different terms have been used to refer to poor awareness in Alzheimer's disease (AD), such as anosognosia, loss of insight, unawareness, impaired self-awareness, denial, and impaired self-consciousness (Markova & Berrios, 2006). Spaletta et al. (Spalletta, Girardi, Caltagirone, & Orfei, 2012) defined anosognosia as "the underestimation of limitations in activities of daily living (ADLs), failure to use compensatory strategies, and a tendency to adopt dangerous behaviours". This is a useful working definition, which not only includes awareness of deficits, but the level of adaptation and negative consequences of anosognosia as well. Starkstein et al. (S. E. Starkstein, Jorge, Mizrahi, & Robinson, 2006) defined anosognosia as the loss or diminished awareness of deficits in activities of daily living (ADLs), behavioural changes, and mood problems. While anosognosia may also apply to more specific domains (e.g. awareness of having an illness), this definition covers the most clinically relevant domains in AD. This article will review the most relevant aspects regarding diagnosis, frequency, clinical correlates, mechanism and treatment of anosognosia in AD. Another aim is to discuss current limitations of empirical research into this condition as well as to

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offer a constructive conceptual criticism to novel and interesting models.

## 2. Method

A detailed search of the literature was conducted using the PubMed services database with the words *AD, anosognosia, insight* and *awareness* spanning the period January 1980 to April 2014. The search using the words *AD* and *anosognosia* produced the higher number of citations ($N = 301$). Of those, 71 were considered of relevance for this review article based on meeting scientific and conceptual criteria (case reports, small case series or replication studies with substandard methodology were not included). Relevant journals were also handsearched, and the references of relevant articles were searched for further publications. Papers reporting empirical findings, proposing conceptualization of anosognosia in AD, or proposing pathogenetic models based on neuropsychiatric or neuropsychological data were chosen for discussion.

## 3. Diagnosis of anosognosia in AD

Three strategies have been used to assess anosognosia in AD (S. E. Starkstein et al., 2006). The *clinician rating of patients' awareness of illness* strategy consists of a routine clinical or semi-structured interview, after which the examiner classifies patients into the categories of full, partial, or no awareness of deficits (Auchus, Goldstein, Green, & Green, 1994; Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Ott et al., 1996; Reed, Jagust, & Coulter, 1993; Verhey, Rozendaal, Ponds, & Jolles, 1993). This diagnostic scheme assumes that anosognosia is a symptom that can be reliably assessed in the context of a clinical interview. Limitations of this strategy are the non-structured quality of the evaluation, the lack of standardised diagnostic criteria, and the unknown validity and reliability of this procedure.

The *prediction of performance discrepancy* strategy is based on the patients' report about their level of performance on a given neuropsychological task (Clare, 2004a, 2004b). Anosognosia is scored as the difference between the patients' estimation of performance and the score obtained on the test. There are conceptual and methodological limitations to this strategy. Anosognosia in AD most often refers to deficits on ADLs and behavioural/mood changes, and not to deficits on neuropsychological tests. The ecological validity of this procedure remains unknown, and it is possible that patients may minimize their functional problems while acknowledging performing poorly on a cognitive test, and vice versa. Another limitation is that lay people may ignore what constitutes a normal performance on a neuropsychological test, and their answers may be influenced by idiosyncratic beliefs or perceived attitudes of the examiner.

Finally, the *patient-caregiver discrepancy* strategy is based on comparing the ratings given by patients about their level of performance on a variety of ADLs and behavioural/mood changes, against ratings provided by their caregivers (Correa, Graves, & Costa, 1996; Mangone et al., 1991; Migliorelli, Teson, Sabe, Petracca, et al., 1995). One limitation is that caregivers' report may be influenced by diverse factors such as burden, stress, and depression. However, Snow et al. (Snow et al., 2004) found a significant correlation between the reports of caregivers and those of clinicians, and significant correlations were reported between caregiver's assessment of deficits and patients' scores on the Mini Mental State Exam (S. E. Starkstein et al., 2006) and anterograde memory tests (Grut et al., 1993; Koss, Patterson, Ownby, Stuckey, & Whitehouse, 1993). Moreover, the reliability and accuracy of information provided by caregivers is strong (Cacchione, Powlishta, Grant, Buckles, & Morris, 2003a, 2003b; Jorm, 1996; Tierney, Szalai, Snow, & Fisher, 1996).

General limitations to any diagnostic strategy for anosognosia in AD are the fact that awareness of deficits is conceptually related to the level of complexity of patients' usual activities, and becoming aware of limitations requires considering one's performance against the context of everyday activities. Therefore, the most accurate way to diagnose anosognosia in AD may consist of an instrument adjusted to each patient's pattern of activities, emotions, behaviour, and relevant social factors, although this may not be feasible in the context of busy practices.

Using the caregiver-patient discrepancy strategy, Starkstein et al. (S. E. Starkstein et al., 2006) developed the Anosognosia Questionnaire-Dementia (AQ-D), a valid and practical instrument to rate anosognosia in AD. The AQ-D is a 30-item questionnaire seeking responses from both patients and their caregivers about the current level of patient's impairment in basic and instrumental ADLs and behavioural and mood changes. This instrument is highly informative and valid for the constructs of both cognitive deficits and behavioural/mood problems in AD (Egede & Ellis, 2010; Spalletta et al., 2012). A factor analysis of the AQ-D produced the factors of anosognosia for deficits on basic ADLs, deficits on instrumental ADLs, depression, and disinhibition (S. E. Starkstein et al., 2006). Anosognosia for deficits on ADLs is already present in the stage of very mild dementia, and greater patient/caregiver discrepancies are found for date recall, spatial orientation, remembering phone calls, understanding conversations, remembering were belongings were left, handling money, remembering appointments, understanding the plot of a movie, and doing clerical work. Starkstein et al. (S. E. Starkstein et al., 2006) defined standardised criteria to diagnose anosognosia using items included in the instrumental ADLs factor. Based on receiver-operating characteristic (ROC) statistics, a cut-off score of four points (i.e. noticeable caregiver to patient discrepancy) on at least four items on the instrumental ADLs domain of the AQ-D showed a sensitivity of 81% and a specificity of 97% against expert clinical diagnosis.

Snow et al. (Snow et al., 2004) developed the Dementia Deficits Scale (DDS) to assess self-awareness of cognitive, emotional and functional deficits in dementia. Parallel forms of the DDS are completed by the patient, clinician, and informant, and this instrument demonstrated adequate reliability and validity. Hardy et al (Hardy, Oyebode, & Clare, 2006) developed the adjusted Memory Awareness Rating Scale (MARSA) based on a similar instrument used in mild dementia (Clare, Wilson, Carter, Roth, & Hodges, 2002). The MARSA includes two components: 1) Both the participant and an informant rate the participant's efficacy in performing several

ADLs that require memory; 2) A comparison of the participant's performance on a memory test, against her/his judgement of performance. More recently, Clare et al. (L. Clare et al., 2012c) examined the utility of vignettes as an indirect method for assessing anosognosia in AD. They found that vignette scores were moderately associated with scores derived from in-depth clinical interviews, but the usefulness of this strategy requires further evaluation.

Two recent studies provide partial validation to instruments that may be used to assess anosognosia in AD, although none of them were specifically designed for this purpose. Dourado et al. (Dourado et al., 2014) examined the psychometric properties of the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD) and reported strong internal consistency. Maki et al. (Maki, Yamaguchi, & Yamaguchi, 2013) assessed the Symptoms of Early Dementia-11 Questionnaire for use in AD, a screening questionnaire for identifying dementia, and validated this instrument against the AQ-D.

In conclusion, there is no canonical method to diagnose anosognosia in AD, and all three strategies discussed above have relevant methodological shortcomings, such as not being ecologically valid, or depending on caregivers' beliefs. The best diagnosis still remains a thorough neuropsychiatric assessment by an experienced clinician in the context of informants available to provide ancillary information about the individual under study.

## 4. Frequency of anosognosia in AD

The frequency of anosognosia in AD is reported to range between 20% and 80% (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991; Migliorelli, Teson, Sabe, Petracca, et al., 1995; Reed et al., 1993; Sevush & Leve, 1993). This wide discrepancy may be due to variability in diagnostic methods, sampling bias, heterogeneous sample sizes (Leicht, Berwig, & Gertz, 2010; Migliorelli, Teson, Sabe, Petracca, et al., 1995; Sevush & Leve, 1993) and the inclusion of AD patients in different stages of dementia. Starkstein et al. (S. E. Starkstein et al., 2006) reported that 10% of patients with very mild dementia had anosognosia, with the frequency increasing to 57% among patients with severe dementia. A longitudinal study by the same group demonstrated an increase in the frequency of anosognosia over time, and similar findings have been reported by others (Aalten et al., 2006; L. Clare et al., 2012b; Mograbi et al., 2012).

In conclusion, empirical evidence suggests that anosognosia becomes more frequent as dementia progresses. Frequencies at each stage depend on the strategy used to diagnose anosognosia and source of patients (e.g. community *vs* memory clinics).

## 5. Correlates of anosognosia in AD

### 5.1. *Disinhibition and dangerous behaviours*

AD patients with anosognosia may engage in activities well beyond their true functional capacity, thus becoming exposed to potentially dangerous events. Starkstein et al. (S. E. Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007) reported that 16% of a series of 278 individuals with AD had dangerous behaviours, with a high risk of physical harm during the month preceding the clinical evaluation. Dangerous behaviours were significantly associated with the presence of anosognosia, but with neither depression nor suicide ideation. Migliorelli et al. (Migliorelli, Teson, Sabe, Petracca, et al., 1995) reported higher scores on mania and pathological laughing scales for AD patients with anosognosia as compared to AD patients without anosognosia, and suggested that anosognosia may be a component of a broader disinhibition syndrome. Starkstein et al. (S. E. Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996) reported a significant association between anosognosia for functional deficits and severity of dementia, whereas anosognosia for behavioural problems was related to disinhibition. Several authors found anosognosia to be associated with disinhibition (Conde-Sala et al., 2013; S. E. Starkstein et al., 1997; S. E. Starkstein et al., 2007; S. E. Starkstein et al., 2006), irritability and anxiety (Conde-Sala et al., 2013; Migliorelli, Teson, Sabe, Petracca, et al., 1995; S. E. Starkstein et al., 2006; Vasterling, Seltzer, Foss, & Vanderbrook, 1995), agitation (Harwood, Sultzer, & Wheatley, 2000; Spalletta et al., 2012), and aberrant motor behaviour (Spalletta et al., 2012). Spaletta et al. (Spalletta et al., 2012) found anosognosia for neuropsychiatric problems to be associated with more severe agitation and apathy, whereas global anosognosia was associated with increased aberrant motor behaviour.

### 5.2. *Depression*

The frequency of depression in anosognosia is present in about 20%–40% in cross sectional samples (S.E. Starkstein, Jorge, Mizrahi, & Robinson, 2005). This variability may depend on various factors, such as severity of dementia, sample bias (community *vs* memory clinic participants), and type of assessment: from depression rating scales such as the Neuropsychiatry Inventory (Conde-Sala et al., 2013), the Neurobehavioural Rating Scale (Horning, Melrose, & Sultzer, 2014), the Cornell Scale for Depression in Dementia (Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005), to structured assessments such as the Structured Clinical Interview for DSM-IV (Migliorelli, Teson, Sabe, Petrachi, et al., 1995). Depression should be diagnosed based on structured clinical interviews and using standardized criteria. Most studies of depression in AD have used depression rating scales, which should be used to rate the severity of depression but not for diagnostic purposes. These limitations also apply to most studies on depression among AD patients with anosognosia. Most studies have found increasing anosognosia in AD to be associated with less severe depression (Conde-Sala et al., 2013; Harwood et al., 2000; Horning, Melrose, & Sultzer, 2013; Kashiwa et al., 2005; Lopez et al., 1994; Sevush & Leve, 1993; Vogel, Waldorff, & Waldemar, 2010). Migliorelli et al. (Migliorelli, Teson, Sabe, Petracca, et al., 1995) found no association between anosognosia and major depression in AD. On the other hand, minor depression was significantly associated with less severe anosognosia, suggesting that minor depression may constitute an emotional reaction to the awareness of functional deficits.

There are few longitudinal studies examining direction of causality between anosognosia and depression. Van Vliet et al. (van Vliet et al., 2013) reported a significant association between more severe anosognosia and less depression in a cross-sectional analysis, but a logistic regression for the 1-year follow-up period failed to show significant effects for the baseline level of awareness and depression severity at follow-up.

### 5.3. *Apathy*

Cross-sectional studies have reported a significant association between anosognosia and apathy (Conde-Sala et al., 2013; Migliorelli, Teson, Sabe, Petracca, et al., 1995; Spalletta et al., 2012; S. E. Starkstein, Brockman, Bruce, & Petracca, 2010; SE. Starkstein et al., 1995a, 1995b). Ott et al (Ott, Noto, & Fogel, 1996) found that both apathy and anosognosia were associated with right temporal hypoperfusion. In an 18-month longitudinal study Starkstein et al. (S. E. Starkstein et al., 1997) found that patients with anosognosia at baseline had a significant increase on apathy scores during follow-up relative to patients without anosognosia at both assessments. The severity of anosognosia and apathy increased over time, suggesting that these phenomena are robust constructs in AD, and that remission is rare. The authors suggested that patients with anosognosia have a poorer adaptation response to their functional impairment than patients without anosognosia. When AD patients with good awareness are faced with increasing functional limitations in their ADLs they may look for and engage in activities that are compatible with their current functional capacities. On the other hand, AD patients with anosognosia may fail to search for alternative activities. These patients may become frustrated and irritable (S. E. Starkstein et al., 2007), loosing motivation for most activities.

Mograbi and Morris (Mograbi & Morris, 2014) found that AD patients showed less awareness of failure on a cognitive task but a similar emotional reactivity as compared to healthy controls, suggesting preservation of implicit awareness in AD. The authors suggested that AD patients with apathy may ignore errors and their consequences given their inability to feel an "affective signature" which may impact on metacognitive systems. Rosen (Rosen, 2011) suggested that motivational factors may affect the level of monitoring, resulting in poor awareness. Events signalling poor performance may then trigger alarm signals in the ventromedial prefrontal cortex, whereas the absence of these signals may lead patients to disregard events as relevant, contributing to anosognosia. These interesting hypotheses deserve further empirical study.

In conclusion, most studies reported a significant association between anosognosia and apathy in AD. Nevertheless, it is important to stress that studies are methodologically heterogeneous, with some using valid and reliable instruments to measure anosognosia and apathy in AD, and others relying on instruments with unclear psychometric attributes.

### 5.4. *Caregiver burden*

Anosognosia is related to caregiver burden in both family members (Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997) and professionals working in day-care hospitals (Al-Aloucy et al., 2011; Clare, Whitaker, et al., 2011). Clare et al. (Linda Clare et al., 2012a) found a significant association between anosognosia, more severe caregiver stress, and poorer quality of relationships. Turro-Garriga et al. (Turro-Garriga et al., 2013) reported that anosognosia accounted for 13% of the total variance of caregiver burden, and impact of anosognosia was most severe on physical and social burden, emotional stress, and dependence. Anosognosia is also associated with greater difficulty controlling the patient, less adherence to pharmacological and non-pharmacological treatment, and early institutionalization (Turro-Garriga et al., 2013).

### 5.5. *Quality of life (QoL)*

AD patients with anosognosia may report a relatively better QoL than patients without anosognosia, but with greater caregiver burden (Turro-Garriga et al., 2013]. On the other hand, anosognosia is also associated with dangerous behaviours (S. E. Starkstein et al., 2007), which may have a detrimental effect on patients' QoL.

### 5.6. *Cognitive deficits*

Lopez et al. (Lopez et al., 1994) reported a significant association between anosognosia and cognitive deficits (primarily executive dysfunction). More severe executive dysfunction among AD patients with anosognosia was also reported by other authors (Michon, Deweer, Pillon, Agid, & Dubois, 1994), but this finding has not been consistently replicated (Migliorelli, Teson, Sabe, Petracca, et al., 1995; S. E. Starkstein et al., 2006). Anosognosia has been reported to be associated with performance on the Trail Making Test (Lopez et al., 1994), the Continuous Performance Test (Mangone et al., 1991), the Word Card Sorting Test (Michon et al., 1994), and part III of the Stroop Test (Kashiwa et al., 2005). Amanzio et al (Amanzio et al., 2013) suggested that discrepant findings among studies may be related to a dissociation between awareness of functional deficits and awareness of behavioural and affective deficits. One of the first studies to demonstrate this dissociation calculated a factor analysis for the AQ-D (S. E. Starkstein et al., 1996). This produced a "cognitive unawareness" factor, which loaded on items of memory, spatial and temporal orientation, calculation, abstract reasoning, and praxis, and a "behavioural unawareness" factor, which loaded on items of irritability, selfishness, inappropriate emotional display, and disinhibition. Thus, discrepant findings may have resulted from using instruments with a narrow scope for anosognosia (e.g. assessing unawareness for cognitive deficits only), as compared to studies using a broader assessment for anosognosia.

Another confounding factor is that executive dysfunction is a heterogeneous construct consisting of different subcomponents (e.g. attention, inhibition, monitoring, planning, task management and coding), and is assessed with a variety of instruments. Amanzio et al. (2013) found associations between some measures of executive dysfunction, but not with deficits on other cognitive domains, such as memory and language. This finding is in line with other studies that found

no association between anosognosia and overall memory performance (Auchus et al., 1994; Michon et al., 1994).

In conclusion, disparities in the association between anosognosia and cognitive deficits may be related to different methods to diagnose and measure the severity of anosognosia, and the heterogeneity of the neuropsychological assessment, ranging from generic cognitive assessments to more detailed studies on specific cognitive domains.

## 6. Mechanism of anosognosia in AD

### 6.1. *Imaging studies*

Studies using single photon emission tomography or positron emission tomography showed a significant association between anosognosia and hypoperfusion/hypometabolism in a variety of brain regions, such as the right frontal lobe (dorsal and inferior gyrus) (Harwood et al., 2005; Salmon et al., 2006; Sedaghat et al., 2010; S. E. Starkstein et al., 1995a, 1995b; Vogel, et al., 2005), medial temporal regions (Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2006; Ott, Noto, et al., 1996; Salmon et al., 2006; Sedaghat et al., 2010), inferior parietal cortex (Ruby et al., 2009; Sedaghat et al., 2010), bilateral frontal cortex (Mimura & Yano, 2006), inferior, medial and orbital frontal cortex and cingulate (Hanyu et al., 2008), superior frontal and orbitofrontal cortex (Martinez-Martin, Frades-Payo, Aguera-Ortiz, & Ayuga-Martinez, 2012; Salmon et al., 2006; Shibata, Narumoto, Kitabayashi, Ushijima, & Fukui, 2008), and right temporoparietal cortex (Ott, Noto, et al., 1996; Salmon et al., 2006).

Three studies used functional MRI (fMRI) to examine the association between brain regional dysfunction and anosognosia in AD. Amanzio et al. (Amanzio et al., 2011) reported reduced activity in the right cingulate, rostral prefrontal cortex, right postcentral gyrus, the temporoparietal-occipital junction, the left temporal lobe, striatum and cerebellum in AD patients with anosognosia during a go/no go task. Zamboni et al. (Zamboni et al., 2013) reported that larger discrepancies between AD patients and caregivers on self-appraisal were associated with lower activation of the medial prefrontal cortex and the left anterior temporal lobe. Jedidi et al. (Jedidi et al., 2013) examined self- and hetero-evaluation of personality in 37 AD patients and found that those with anosognosia had significantly lower activity in the dorsal prefrontal cortex.

Salmon et al. (Salmon et al., 2006) reported a significant association between impaired self-evaluation and hypometabolism in orbitofrontal, medial temporal, and temporoparietal regions. They suggested that medial temporal dysfunction may lead to impairments in the comparison between current information on cognition and personal knowledge, orbitofrontal cortex dysfunction may produce deficits updating the qualitative judgement associated with cognitive abilities, and dysfunction of the temporoparietal junction may be related to impairment of self-referential process and perspective-taking. Other studies proposed impaired self-awareness resulting from medial prefrontal cortex dysfunction (Zamboni et al., 2013), deficits in processing self-significant information resulting from cingulate and temporoparietal dysfunction (Amanzio et al., 2011), and impaired third perspective taking resulting from dorsal medial prefrontal cortex dysfunction (Jedidi et al., 2013).

Some of these discrepancies may result from conceptual misunderstandings. For instance, Salmon et al (Salmon et al., 2006) suggested that anosognosia may be a deficit to see oneself in terms of a third-person perspective. The question arises as to whether it is possible to have such a perspective devoid of the agent's beliefs and expectations. In related publications, Ruby et al (Ruby et al., 2009) suggested that behavioural awareness requires the agent to infer the mind of other persons, but this is also conceptually unclear. Awareness of one's behaviour requires a proper understanding of contextual clues, such as the behaviour of other individuals (e.g. the agent's aggressive behaviour resulting in the interlocutor leaving the room in disgust, expressing anger in his facial demeanour, etc.). In fact, Ruby's study showed that AD patients were impaired in the "third-person perspective taking" irrespective of the target (self or the relative). This finding suggests that third-person perspective taking is not specifically related to self-assessment, but is a more generic deficit in the context of dementia. Other confounders are inherent to the method used to elicit third-person perspective (i.e. asking participants to answer whether according to a third person they have specific personality traits). Factors such as whether patients were explicitly told to have those attributes, remembering being told, the third-person own personality features and her/his disposition towards the patient may all influence the results.

In conclusion, there is no common pattern emerging from the imaging studies described above. Discrepancies may be explained by different imaging techniques such as using the region of interest method versus voxel-based analysis, different strategies used to diagnose anosognosia, small sample sizes, different severities of cognitive and functional impairment, use of anticholinesterase medication, and variability in frequencies of behavioural and psychiatric disorders. Analysis of the methodology used in the most recent imaging studies of anosognosia in AD may illustrate the extent of these confounders. Amanzio and co-workers (Amanzio et al., 2011) included 29 AD patients and 29 caregivers. Exclusion criteria were use of psychotropic medication, presence of major psychiatric disorders, and a Hachinski Ischemic score lower than 5. AD patients had an MMSE score ranging from 19 to 24. Anosognosia was assessed with the AQ-D, and a response inhibition task was assessed during fMRI. Image analysis was carried out using co-registration and voxel-wise group analysis, and images were acquired on an 1.5T device. Zamboni et al. (Zamboni et al., 2013) included 17 AD patients and no detailed inclusion/exclusion criteria were provided, but none of the patients were on cholinesterase inhibitors. Anosognosia was assessed based on questions about patients' themselves and their partners. Imaging was carried out on a 3T device, and image analysis was based on the boundary-based registration method. Ruby et al. (Ruby et al., 2009) included 14 patients with mild AD, all on cholinesterase inhibitors and with a history of substance abuse as the exclusion criterion. Participants were asked to make personality judgements concerning themselves and their relatives, taking their own or their relative's perspective. fMRI's were carried out with a 3T device and data was analysed with statistical parametric mapping (SPM). Salmon et al. (2006)

assessed 209 patients with AD, without detailing inclusion/exclusion criteria. Anosognosia was assessed with an experimental questionnaire, and imaging was carried out with FDG-PET and SPM. Jedidi et al. (Jedidi et al., 2013) included 37 AD patients, without specifying inclusion/exclusion criteria. Anosognosia assessment was based on patient to caregiver discrepancy scores on an instrument measuring personality traits, and imaging was carried out with FDG-PET and SPM. Finally, Shibata et al. (Shibata et al., 2008) examined with FDG-PET 29 AD patients on no psychotropic medication or cholinesterase inhibitors, and an MMSE less than 18. Anosognosia was calculated based on discrepancy scores for memory function between patient and caregiver.

### 6.2. Theoretical models

Early theories on the mechanism of anosognosia in AD were presented by McGlynn and Schachter (Grut et al., 1993; McGlynn & Schacter, 1989), who suggested that anosognosia for specific cognitive deficits occurs with disconnection of a "conscious awareness system" (CAS) from individual cognitive modules, while damage to the CAS may result in global anosognosia.

Morris et al. (R.G. Morris, 2004) proposed the "cognitive awareness model" (CAM), which posits that new information is monitored by comparator mechanisms that contrast incoming data with representations stored in a "personal database" (PDB). The output of this comparison allows the PDB to be updated in case of mismatch, and the product of this process is relayed via a "metacognitive awareness system (MAS)" to provide conscious decision-making. The authors suggested that whereas individuals with "mnemonic anosognosia" are able to detect cognitive failures and demonstrate awareness of failures, they are unable to encode those failures into semantic memory, relying on outdated semantic representations of their abilities. Supporting empirical evidence was provided by Ansell and Buck (Ansell & Bucks, 2006) who found that AD patients tend to overestimate their performance on memory tests, suggesting a loss of recalibration of accuracy during the time interval between the presentation of the stimuli and recall. Loss of autobiographical memory in AD (Irish, Lawlor, O'Mara, & Coen, 2011) may further impair evaluation of expected ability. This model has been refined in subsequent publications. Mograbi et al. (Mograbi, Brown, & Morris, 2009) suggested that anosognosia in AD may be explained by the typical pattern of memory deficits in AD [i.e. deficits in recent memory with relative sparing of older information (Greene, Hodges, & Baddeley, 1995)] leading to an outdated sense of self (Klein et al., 2009). In patients with anosognosia the encoding of new information is impaired, and improvement through feedback mechanisms is limited and short-lived. Thus, reflection about the self remains unmodified in time due to loss of memory updating (Ansell & Bucks, 2006), and personal evaluation becomes inaccurate. In this context, evaluation of self-performance is based on pre-morbid self-knowledge only, resulting in a "petrified self" (Mograbi et al., 2009). Morris and Mograbi (Robin G. Morris & Mograbi, 2013) have proposed that anosognosia in dementia is caused by loss of autobiographical memory resulting in retrieval difficulties and lack of consolidation of new material about self-ability. Poor recollection of success or failure may lead to an inaccurate sense of self-ability and loss of recalibration of personal information. Deficits in metamemory may also account for anosognosia in AD (Cosentino, Metcalfe, Butterfield, & Stern, 2007; Moulin, Souchay, & Morris, 2013; Souchay, Moulin, Clarys, Taconnat, & Isingrini, 2007) as faulty memory monitoring may impair personal memory updating. In their latest elaboration of the CAM, Morris and Mograbi (Robin G. Morris & Mograbi, 2013) have posited a "central cognitive comparator" which functions under executive control and detects current functional deficits as compared with stored information. Deficits of this central mechanism may result in "executive anosognosia."

Rosen (Rosen, 2011) proposed a model for anosognosia in AD that includes dysfunction of emotional mechanisms. Similar to the CAM, this model consists of a monitoring system that compares current against expected performance. New to this model is the suggestion that emotion influences motivational factors, affecting the degree of monitoring. Whenever discrepancies are detected, activity in emotion modules marks the event with a level of importance. Events are evaluated based on discrepancies and their emotional significance, and this information is recorded in long-term memory and used to update the representation of one's abilities. Events signalling poor performance may trigger emotional alarm signals, and the absence of these signals may produce anosognosia by allowing individuals to disregard these events when evaluating their abilities. The authors tested this model in a study that examined associations between self-appraisal of performance on cognitive tests and regional grey matter volume. They found a significant association between self-appraisal accuracy and grey matter volume in the right ventromedial prefrontal cortex, a region involved in self-monitoring (Rosen, 2011).

Clare (Clare, 2003) proposed a biopsychosocial model for anosognosia. When coping with the impact of dementia, patients experience a tension between the need to preserve a sense of self and the need to integrate new experiences and adjust behavioural responses in consequence. In this model awareness is influenced by beliefs, norms, and expectations interacting with motivational factors (Clare, Markova, Roth, & Morris, 2011), whereas the social context facilitates or hinders the manifestation of awareness. These authors suggested four levels of awareness, which are determined by cognitive capacity and psychosocial and environmental influences: (1) *sensory registration*: simple internal representations reflect the patient's capacity for attentional resources to be directed to an object, leading to appraisal and/or behavioural response; (2) *performance monitoring*: ongoing task performance is monitored as it occurs, comparing expected and actual outcomes, identifying errors, and evaluating success; (3) *evaluative judgement*: general awareness of specific functional deficits is influenced by beliefs, social stereotypes and emotional responses; and (4) *metarepresentation*: this level provides the most complex aspect of awareness, incorporating self-reflection and the ability to consider the perspective of others.

### 6.3. Conceptual criticism

The models discussed above are important to further our understanding of the phenomenon of anosognosia in AD.

Nevertheless conceptual criticism may help to clarify and refine these or future models.

The first conceptual problem is the mechanism by which representations of personal information are stored in a PDB. None of the models clarifies what these putative representations consist of or how personal information is encoded. Perhaps a task failure such as "Getting lost when reaching the town" (from Morris & Mograbi, 2013) is "easy" to encode, but it is unclear how representations may encode logical connectives (e.g. "*If* I have memory problems, *then* I should better consult my doctor"), or qualifiers (e.g. "*Some* of my memory problems are *too* severe to be related to ageing alone").

It may still be suggested that anosognosia may result from deficits in comparing new against old representations (e.g. laughing at a funeral for the first time as compared with previous behaviour in the same context). The problem with this theory is that comparison of representations requires a superior instance indicating a mismatch, which may lead to a regress. Moreover, representations could be interpreted in different ways (e.g. laughing at a funeral may be a representation of behaviours that should *not* be enacted).

Most models include a comparator system, which evaluates differences between incoming information and representations of personal abilities stored in a PDB. Thus, the comparator has to "select" from the PDB those representations that are congruent with incoming data. The question arises as to how the comparator "knows" which representations to select. If the comparator already has this knowledge, the PDB becomes redundant. It may be argued that the comparator has only a "shallow" knowledge of the representation to be selected; however, this is still to accept that the comparator has certain knowledge, and therefore, internal representations. Unfortunately this results in an infinite regress, since the comparator's own representations have to be compared by a superior instance.

The comparator's job is to determine a potential mismatch between incoming information and stored representations. Therefore, it can only feed the MAS (R.G. Morris, 2004) with information regarding differences, but devoid of judgement value. It is unclear which instance in the model determines that a putative mismatch has a negative valence, and what mechanism is implied. If the MAS assign value, then this system has to be endowed with its own comparator and memory mechanism, falling again into an infinite regress. Rosen's (Rosen, 2011) model provides an option in which mismatches are "marked" with emotions that trigger an alarm system. However, questions then arise as to which instance provides emotional values and on what grounds, and which emotions are selected and on what grounds. Common to all these models is the problem of how they account for novel events, such as a patient showing disinhibited behaviours for the first time. In this instance, there is no representation in the PDB against which current behaviour can be compared (e.g. representations of "not yet disinhibited" cannot be conceptually justified).

This is just a brief account of conceptual problems with current models of anosognosia in dementia. A more detailed analytical discussion may help to develop more conceptually robust models.

## 7. Treatment of anosognosia in AD

Anosognosia may delay the diagnosis of dementia by preventing patients from seeking medical evaluation, and may also impede interventions (Rosen, 2011). The need for constant supervision may impose an emotional and financial burden upon families, and management of anosognosia in AD should follow a holistic approach, including patients, caregivers, families and health professionals.

There are no randomized controlled trials of psychotherapy for anosognosia in AD. Al-Aloucy et al. (Al-Aloucy et al., 2011) suggested that interventions such as cognitive stimulation, cognitive behavioural therapy (CBT) for the education of patients and caregivers, and behavioural activation may enhance memory functions and contribute to a better updating of self-image. Based on the CAM model, Morris & Mograbi (2013) suggested that patients with executive anosognosia may benefit from treatments focused on enhancing error monitoring, whereas patients with mnemonic anosognosia may benefit from memory rehabilitation techniques enhancing recollection and consolidation of current personal knowledge. Clare et al. (Clare, Markova, et al., 2011) suggested that interventions should focus on negotiating areas of common ground, providing support to facilitate improvements in coping style. They also suggested that support and psychotherapy groups may help improving awareness in early dementia (Logsdon et al., 2010); while the provision of contextual cues and environmental support may benefit patients in the moderate and severe stages of the illness. Nevertheless, as recommended by Mograbi and Morris (Mograbi & Morris, 2014), exposing AD individuals to their limitations should be carried out with care, as some patients may become depressed.

## 8. Conclusions

Anosognosia is a frequent phenomenon in AD and has great clinical impact, as patients with anosognosia may engage in dangerous and disinhibited behaviours. There is a significant association between anosognosia and more severe dementia, higher caregiver burden, more severe apathy, and less severe depression and anxiety. No specific profile of neuropsychological deficits has been associated with anosognosia in AD. Several models have been proposed to explain anosognosia in dementia, but relevant conceptual issues limit their heuristic value. Future models of anosognosia in AD should examine converging causes for anosognosia, including not only dysfunction in specific brain networks but also relevant contextual factors such as previous personality, supports available to the patient, and psychiatric comorbidity among others. Finally, psychotherapy and support techniques have been suggested for the treatment of anosognosia in AD, but adequate randomised controlled trials are still lacking.

## Relevant conflict of interest

There is no conflict of interest related to this article.

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