Curr Neurol Neurosci Rep (2016) 16: 77
DOI 10.1007/s11910-016-0684-z

BEHAVIOR (H KIRSHNER, SECTION EDITOR)

Anosognosia in Dementia

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Published online: 20 July 2016

Abstract Progressive decline in memory (and other functions) is the defining feature of late-life dementia but affected individuals are often unaware of this impairment. This article reviews recent research on anosognosia in dementia, including methods of assessing anosognosia, its prevalence and developmental course in dementia, its occurrence in different forms of dementia, neuroimaging findings, and hypothesized component mechanisms. The results suggest that anosognosia is eventually exhibited by nearly all persons with dementia. Its occurrence is robustly associated with common dementia-related pathologies and damage to memory and self-referential brain networks and their interconnections.

Keywords Anosognosia · Metacognition · Memory awareness · Subjective memory · Dementia · Frontotemporal dementia

This article is part of the Topical Collection on *Behavior*

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Introduction

The term anosognosia was initially used to describe the unawareness of impairments due to focal lesions of the brain [1]. It now refers more broadly to impaired awareness of the functional consequences of medical conditions. Although anosognosia is observed in a wide range of neurologic disorders, it is especially common in dementia. The aim of this article is to review current knowledge on anosognosia in dementia with an emphasis on recent research.

A key feature of anosognosia in dementia that distinguishes it from anosognosia following focal lesions is its relative lack of specificity [2]. That is, although awareness of impairment may vary across functional domains [3], affected persons tend to underestimate their deficits in multiple domains compared to more isolated areas of unawareness with focal lesions. Because most research on anosognosia in dementia has been on awareness of memory impairment, the present review will focus exclusively on memory awareness unless otherwise noted.

Despite years of research on anosognosia in dementia, the basis of the syndrome is not well understood. A fundamental problem has been that approaches to assessing anosognosia have widely varied, making it difficult to integrate findings across studies. In addition, dementia develops insidiously over many years but most research has either used a cross-sectional design or a longitudinal design with a relatively short follow-up period, limiting knowledge of how the problem develops within individuals. As a result, there has been a little consensus on how often anosognosia occurs in dementia or on its antecedents, consequences, or neural bases. Nonetheless, advances in neuroimaging and theoretical models of anosognosia in dementia have substantially enhanced current knowledge about loss of memory awareness in dementia.

The remainder of this review is divided into five sections. We first consider methods of assessing anosognosia. We then examine the prevalence and developmental course of anosognosia in dementia, its relation to dementia subtypes, neuroimaging research, and underlying component mechanisms.

Assessment of Anosognosia

In anosognosia, there is a mismatch between the functional consequences of a condition and self-appraisal of one's function. Therefore, the measurement of anosognosia requires both self-report about level of function and some other measure of function that does not rely on self-report. It is generally assumed that objective assessment entails less measurement error than self-report, indicating the importance of using a gold standard objective measure.

There have been a variety of approaches to assessing awareness of memory functioning. The most common method is to ask the affected individual and a knowledgeable informant to rate the affected person's memory. Self-ratings of memory that are substantially more favorable than informant ratings are indicative of anosognosia. There are problems with this approach, however. The most fundamental drawback is that informant ratings of memory and other cognitive functions are not very accurate [4, 5]. Informant ratings of memory and cognition can discriminate groups with dementia from cognitively healthy older people [6], but most late-life cognitive decline progresses slowly over a period of years [7, 8] and these gradual changes are difficult to reliably capture with informant report. There is also evidence of systematic bias in informant ratings. Thus, levels of distress and cognitive function in the informant have been associated with informant ratings of behavior in persons with dementia [9–11].

Another approach to assessing awareness of memory function is to contrast the affected person's self-report about memory with his or her performance on memory tests. Self-report and performance scores can be converted to a common scale to facilitate comparisons. One implementation of this approach is to compare global memory ratings (e.g., How often do you have trouble remembering things? Never, rarely, sometimes, often, or very often) with the performance on one or more standard tests of episodic memory to provide an overall index of memory awareness [12, 13••]. Another implementation of this method is to assess the awareness of performance on a specific memory test. This may be done before or after test administration and focus on overall test performance [14] or on specific aspects of metacognitive knowledge such as feeling of knowing, ease of learning, and judgment of learning [15]. The main advantage of this approach is that performance testing is widely recognized as the gold standard for assessment of memory functions. Global applications provide an overall measure of mnemonic awareness. Local probes provide a means of decomposing anosognosia into components, though the associations between global and local awareness measures need further investigation [16].

A final approach to assessing awareness of memory functioning has been to rely on a global rating by an experienced clinician following an evaluation that presumably includes interview data and performance testing of memory and cognition [17–19]. This method potentially has access to all of the data used in the previous approaches. However, strong disadvantages are that the absence of an actuarial method of integrating the data is likely to increase error in judgments of anosognosia, make between study comparisons difficult, and limit insight into components of memory awareness.

In summary, there has been considerable heterogeneity in how investigators have tried to assess anosognosia. It is important to use psychometrically sound objective and subjective behavioral measures and to systematically combine this information. Deviation from these objectives increases measurement error which has probably contributed to inconsistent findings in much of previous research on anosognosia in dementia [9, 14, 20, 21].

Awareness of Memory Function in Old Age

To better understand the awareness of memory function in dementia, we first consider subjective perception of memory function in older persons without dementia. Meta-analyses of cross-sectional studies suggest that higher subjective ratings of memory are related to higher levels of performance on objective memory tests, but the effect sizes are quite small [22, 23]. The results of longitudinal research have been mixed. Some studies have found little evidence that change in objective memory is related to change in subjective memory [24–26]. However, evidence of a positive correlation between change in objective and subjective measures of memory has also been reported, particularly in more recent studies [13••, 27–30]. It is also noteworthy that lower level of subjective memory is associated with higher risk of developing dementia [31, 32] and higher level of Alzheimer's disease pathology on postmortem examination [32, 33].

Research to date, therefore, establishes that older people without dementia can make global judgments about their memory that correspond to objective measurements of memory function. However, the correspondence is not very close, with nearly all studies suggesting less than 10 % of the variance in objective and subjective measures is shared. The weak correspondence between subjective memory appraisal and objective memory performance in cognitively healthy individuals indicates that detecting a diminished level of correspondence in persons with dementia is likely to be challenging.

Anosognosia is commonly observed in persons with dementia, with the behavior identified in approximately 40 % in some studies [34, 35]. Anosognosia has also been described in mild cognitive impairment [36–38], a precursor to dementia, though less often than in dementia [35]. However, there is no secure agreement on the prevalence of anosognosia in these syndromes, likely related to several factors. First, most anosognosia research has been conducted on small selected groups of patients identified in health care settings. Second, as previously noted, approaches to assessing anosognosia have varied. Third, there is little consensus on how severe the unawareness must be or how many domains must be affected to warrant the label of anosognosia.

Another challenge in studying anosognosia in dementia is the chronic, progressive nature of the condition. Thus, it may be less important to know the prevalence of anosognosia in dementia than to know when in the temporal course of dementia it characteristically occurs and what proportion exhibit the behavior at some point in the disease course. A longitudinal design is need to address these issues. Perhaps the most basic question is whether the level of anosognosia increases over time in persons with dementia. Some longitudinal studies have reported declining awareness in dementia [13••, 34, 39, 40], but other studies have observed mixed results [41] or no change [42–47]. The inconsistent findings are likely due in part to methodological shortcomings in some of these studies (<100 participants [34, 39–42, 44–47]; <2 years of follow-up [34, 39–46]; rate of follow-up participation low [34, 40, 47]; or indeterminate [39, 41–46]). In addition, with few exceptions [13••], these studies focused exclusively on prevalent dementia though current evidence suggests that dementia is typically preceded by a decade or more of gradual cognitive decline [7, 8, 48]. It is likely that understanding anosognosia in dementia will require at least some observation during the prodromal period preceding the dementia diagnosis.

To our knowledge, only one longitudinal study examined anosognosia in incident dementia [13••]. Participants were 239 older persons without cognitive impairment at enrollment who developed dementia during a mean of more than a decade of follow-up. At each annual evaluation, memory test performance was regressed on global perceptions of memory with the residuals serving as a longitudinal measure of memory awareness. Memory awareness was stable until a mean of 2.6 years before dementia was diagnosed at which point it sharply declined. Individual differences were evident in the onset of decline in awareness and in the rate at which awareness declined, but nearly all of affected individuals exhibited a substantial loss of awareness.

In summary, therefore, it appears that declining awareness of memory impairment, arguably the principal manifestation of dementia, is a more or less inevitable feature of the condition. Individuals differ less in whether they lose awareness than in when and how rapidly the loss occurs. An important implication of this observation is that anosognosia in dementia is a form of cognitive dysfunction that reflects an incapacity rather than an unwillingness to acknowledge a problem. That is, it represents a further erosion of cognitive ability rather than an active avoidance of reality.

Dementia Subtypes

Anosognosia has been described in virtually all forms of dementia [49–52]. Descriptions of frontotemporal dementia suggest that anosognosia is particularly prominent in this condition [49]. However, the frequent observation that awareness is more impaired in frontotemporal dementia than in Alzheimer's disease [14, 15, 53] is difficult to interpret because early loss of insight may contribute to a diagnosis of frontotemporal dementia [49]. Even if anosognosia is more common in frontotemporal dementia than Alzheimer's disease, the contribution of the sign to differential diagnosis is likely to be limited by the vast disparity in the prevalence of the two conditions.

A postmortem neuropathologic examination provides a means of evaluating the contribution of specific pathologic conditions to anosognosia that avoids the potential bias associated with antemortem clinical classification of dementia subtypes, but few studies have adopted this approach. In one that did, 385 older participants in a longitudinal cohort study died and underwent a brain autopsy and uniform neuropathologic examination [13••]. Decline in memory awareness proximate to death was associated with three dementia-related pathologies: transactive response DNA-binding protein 43 pathology, tau tangles, and gross cerebral infarcts. No decline in memory awareness was observed in the absence of these lesions. Findings were comparable in groups with and without dementia.

In summary, current clinical data suggest that anosognosia occurs in diverse dementia subtypes. It is especially common in frontotemporal dementia, but it is uncertain whether this is because unawareness impacts clinical classification or is an intrinsic manifestation of the condition. Clinical-pathologic research suggests that common dementia-related pathologies account for most of late life anosognosia.

Neuroimaging

Neuroimaging procedures have been used to investigate the pathophysiologic mechanisms underlying memory unawareness in dementia. Although there have been relatively few studies and sample sizes have generally been small, some important findings have begun to emerge.

Consistent with the global nature of anosognosia in dementia, previous reviews have concluded that structural and

functional changes in multiple brain regions are associated with anosognosia in dementia [54, 55]. Much research has focused on frontal and midline structures that support self-referential processing. Thus, in one study using functional MRI, there was less activation in prefrontal cortex and posterior cingulate cortex during a self-referencing task in participants with less awareness of deficits [56]. These functional changes in brain regions associated with self-awareness are supported by structural MRI research. One study found that self-awareness among older persons with diverse neurodegenerative conditions was related to atrophy in dorsal frontal regions that support attention and orbitofrontal and subcortical areas involved in maintaining self-knowledge [57]. Consistent with much previous research, these findings were more pronounced for the right hemisphere than the left. Other studies have implicated the right insula [58] and right cingulate cortex [59].

Further insight into the neural mechanisms underlying memory unawareness in Alzheimer's disease is provided by a recent study [60•]. A memory unawareness index was associated with hypometabolism in orbitofrontal and posterior cingulate cortices based on resting state fluorodeoxyglucose positron emission tomography. Then, using resting state functional MRI and orbitofrontal cortex and posterior cingulate cortex as seed regions, memory unawareness was shown to be associated with decreased intrinsic connectivity of these regions with medial temporal lobe. These observations suggest that unawareness of memory impairment in dementia reflects not only damage to memory and self-referential networks in the brain but also to the connections between these networks.

Components of Anosognosia

The cognitive mechanisms contributing to anosognosia in dementia remain uncertain but most descriptive models hypothesize that two broad processes are involved [2, 61–64]. First, knowledge about one's memory skills can be objectively measured by eliciting feeling-of-knowing ratings and ease-of-learning judgments. Research suggests that these metamnemonic monitoring processes are frontally mediated [49, 61, 62] and generally impaired in Alzheimer's disease [15, 21, 49, 65] and frontotemporal dementia [15, 49, 53]. Second, a central feature of nearly all dementia syndromes is the inability to maintain an enduring record of personal experience. Thus, even if affected persons accurately monitor their mnemonic experiences, they are likely to forget much of them. Research on individuals with an isolated amnesia suggests that anosognosia is less likely if damage is confined to the medial temporal lobe and more likely if frontal regions are also involved [61, 62]. Whether those with dementia fail to adequately monitor their mnemonic behavior, fail to remember it, or both, the result is that knowledge about their memory and cognitive skills is not being updated and judgments about memory are apt to be based on vague normative expectations rather than personal experience [66]. This may explain why among those with dementia, younger persons overrate their memory more than older persons [13••].

Although psychosocial factors have been hypothesized to contribute to anosognosia in dementia [20], published data are sparse and inconclusive. Most studies have examined the cross-sectional association of anosognosia with common neuropsychiatric symptoms of dementia such as apathy and depression. Longitudinal studies are needed that assess psychosocial factors prior to dementia onset and test whether they predict the onset and progression of anosognosia. Current evidence suggests that virtually all persons with dementia develop some degree of memory unawareness and that memory unawareness does not develop in the absence of dementia related pathology [13••], making it unlikely that psychosocial factors strongly impact the onset or progression of anosognosia in dementia.

Conclusions

Declining awareness of memory impairment and other functional limitations is part of the natural history of late-life dementia and represents a cognitive incapacity rather than unwillingness to acknowledge a problem. Longitudinal clinical-pathologic research suggests that nearly all persons with dementia eventually develop anosognosia and that common dementia-related pathologies account for most of the variability in anosognosia. The syndrome is described in all forms of dementia but is an especially prominent and early feature of frontotemporal dementia. In neuroimaging research, anosognosia in dementia has been linked to structural and functional changes in memory and self-referential brain networks and their interconnections. Further research on anosognosia in dementia is needed, particularly population-based studies to more securely establish its prevalence, antecedents, and consequences and longitudinal neuroimaging studies to further clarify its pathophysiology.

Acknowledgments This work was supported by the National Institutes of Health (R01AG34374, R01AG33678, P30AG10161, RF1AG22018).

Compliance with Ethical Standards

Conflict of Interest Robert S. Wilson, Joel Sytsma, Lisa L. Barnes, and Patricia A. Boyle declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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