Functional Outcome in Delusional Alzheimer Disease Patients

A Systematic Review

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Key Words

Delusions · Psychosis · Elderly · Dementia · Alzheimer's disease · Function · Activities of daily living, independent

Abstract

Background: In spite of the prevalence of delusions in Alzheimer's disease (AD) and their association with poor outcomes, there has been little study of the impact of delusions on real-world functioning. **Method:** A number of databases, including Psychlit and Medline, were searched using the keywords: delusions, functional outcomes, activities of daily living, dementia, and Alzheimer's disease. Studies were included in the review if they were in English, restricted to patients with AD, and addressed delusions and function. **Results:** The review yielded a total of 6 studies, 3 of which showed a correlation between delusions and real-world functioning and 3 of which did not. **Conclusion:** A critical analysis of the existing studies suggests that there may be an association between delusions and impaired real-world functioning. We believe that 2 of the 3 negative studies did not show an association due to issues relating to study design and the use of measures insensitive to executive impairment. This review highlights the future need for more scientifically rigorous studies to clarify this association, so as to ultimately improve treatment outcomes for patients.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative condition associated with changes in cognition, real-world functioning and behaviour. Many studies have examined the impact of various factors on functional impairment in AD. One of the most extensively studied variables has been cognitive performance itself, with functional performance correlating with a decline in cognitive performance [1–4]. The majority of studies have shown a non-linear relationship between cognition and real-world functioning, suggesting that while a relationship exists, other important factors may modify this relationship.

Other studies have attempted to determine which neurocognitive factors are most predictive of functional impairment. More recent studies have implicated certain neuropsychological deficits, most significantly executive impairment [5–8]. Intact executive cognitive processing is required to perform many daily functions, such as planning, organizing and multitasking. Royall et al. [7, 8] studied the impact of executive impairment on real-world functioning, both cross-sectionally and prospectively, in a large cohort of community-dwelling seniors. The results showed that executive impairment was independently associated both with the presence of functional impairment and with the rate of decline specifically in instrumental activities of daily living (IADL) after con-

trolling for other variables that could potentially affect real-world functioning. Swanberg et al. [6] conducted a retrospective study and discovered that AD patients with greater executive impairment, as measured by a combination of cancellation tasks and the maze subtest from the ADAS-Cog, had worse function a year later when compared to AD patients with less executive impairment. Evidence for the impact of other neurocognitive variables has been less robust. Edwards et al. [9] found constructional apraxia correlated with increasing functional impairment among outpatients with AD. The role of visuospatial impairment has been less clear, with 1 study showing a correlation [10] and 1 study [11] which showed no effect. Similarly, the impact of memory is inconclusive, with a recent study suggesting a correlation with semantic memory, but no impact of auditory-verbal short-term or episodic memory on functional performance [10].

Real-world functioning in AD may also be impaired by a number of non-cognitive factors. As older patients often develop AD, other factors related to aging such as physical or sensory impairment may play an indirect role. AD is also associated with the development of a number of psychiatric symptoms that may contribute to functional impairment. Both the presence of psychosis and depression in the absence of dementia may be associated with functional decline. Few studies have examined this phenomenon in AD patients, but in those that have, a relationship has been established [12–14], especially when combined with cognitive factors. As most behavioural symptoms emerge with increasing cognitive decline, it has been difficult in these studies to separate out how much decline can be attributed to the symptoms themselves and how much can be attributed to the associated decline in cognition.

Delusions are well documented in AD, with an estimated prevalence of 36% [15]. Incidence rates are more controversial as many of the studies that examined incidence did not differentiate delusions from hallucinations when evaluating psychotic symptoms. This distinction is of paramount importance given that it is now well understood that delusions and hallucinations have a separate neuroanatomical basis [16–18]. However, Paulsen et al. [19] did report a 1-year incidence rate of 20% for psychosis. Previously published studies have also suggested that delusions, like many neurobehavioural symptoms in dementia, may fluctuate [20]. Delusions, in addition to being common, are clinically important symptoms in AD as studies have shown them to be associated with a number of adverse outcomes, including increased caregiver stress and premature institutionalization [21, 22]. Studies

linking delusions to functional performance, however, are lacking.

There are a number of potential reasons why delusions might be expected to be associated with worse real-world functioning. Delusions are often associated with other neurobehavioural symptoms, such as depression and hallucinations, which may also be linked to poor functional performance. Studies to date have suggested that AD patients with delusions are likely to progress more rapidly when compared to AD patients without delusions [19], suggesting as well more rapid functional decline. Some investigators have even suggested that AD patients may be empirically divided into separate categories based on the existence of behavioural symptoms such as delusions or psychosis [23]. Specifically, Ropacki and Jeste [15] have suggested that Alzheimer patients with delusions should be regarded as a more aggressive subtype of the disease, given the association with more moderate cognitive impairment and more rapid cognitive decline. Others [18] have suggested that this may not be the case given that delusions may commonly co-exist with other behavioural symptoms and are unlikely to occur in isolation. One of the most compelling arguments, which may explain both the link to poor functional performance and more rapid cognitive decline, is the relationship between delusions and frontal lobe functioning. As discussed, real-world functioning in AD appears very much linked to executive cognitive processing. Delusions have been linked neuroanatomically, in many studies, to abnormalities in the frontal lobes. Binetti et al. [17] compared CT scans of AD patients with and without delusions and found a significant difference in the number of frontal lobe white matter lesions among the delusional AD patients compared to non-delusional controls. Functional neuroimaging studies conducted using SPECT scans have demonstrated hypoperfusion in the frontal lobes among delusional AD patients when compared to age- and disease-matched non-delusional controls [16, 24]. Kotrla et al. [16] showed relatively greater hypoperfusion in the left frontal lobe compared to the right, while Mega et al. [24] also showed hypoperfusion in the frontal cortex as well as the adjacent parietal and subcortical structures. A recent PET study conducted by Sultzer et al. [25] examined cerebral glucose metabolism in AD patients with delusions, and concluded that delusional severity may be linked neurophysiologically with changes in the right prefrontal cortex. Neuropathological studies have confirmed these findings, suggesting a higher density of senile plaques in the frontal lobes of AD patients with delusions compared to age- and disease-matched controls [26], specifically in

Table 1. Delusions and functional outcome studies

Journal citation	Study design	Psychiatric scales	Outcome
Green et al. [33]	prospective study of 149 patients evaluated at multiple memory clinics in New York City	ADAS-NC	after controlling for the variance associated with cognitive impairment, there was no significant correlation between the presence of delusions and functional impairment as measured by the PSMS and IADL scales
Harwood et al. [34]	prospective study of 114 AD patients evaluated consecutively at an outpatient memory disorders clinic	BEHAVE-AD, RMBPC, BDS, MMSE	after controlling for the variance associated with MMSE, delusions correlated with function ($p < 0.05$) as measured by the BDS
Tekin et al. [35]	retrospective study of 143 outpatients with probable AD	FAQ, NPI, MMSE, CIRS-G	function as measured by the FAQ correlated significantly with the NPI and 9 of the 10 subscores, including delusions ($p < 0.05$)
Mok et al. [36]	retrospective study of 100 outpatients with Alzheimer's disease seen at the Memory Clinic of Queen Mary Hospital	CDR, NPI, MMSE, ADL, IADL	hallucinations and disinhibition scores correlated inversely with ADL, while hallucinations and aberrant motor activity correlated inversely with IADL
Weiner et al. [35]	retrospective database study of 100 autopsy-confirmed AD cases	CDR, MMSE	no significant correlation between the CDR score and delusions ($p = 0.54$)
Liu et al. [38]	prospective study of 142 consecutive AD patients from an outpatient memory disorders clinic	CDR, Barthel Index, Alzheimer's Deficit Scale, BEHAVE-AD	presence of delusions, as measured by the BEHAVE-AD, was significantly correlated with function, as measured by the Barthel Index ($p < 0.05$)

ADAS-NC = Alzheimer's Disease Assessment Scale (non-cognitive subscale); PSMS = Physical and Self-Maintenance Scale; IADL = Lawton's Instrumental Activities of Daily Living; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; RMBPC = Revised Memory and Behavior Problem Checklist; MMSE = Mini Mental State Exam; FAQ = Functional Activities Questionnaire; NPI = Neuropsychiatric Inventory; CIRS-G = Cumulative Illness Rating Scale-Geriatrics; CDR = Clinical Dementia Rating Scale; ADL = Barthel Activities of Daily Living.

the mid-frontal and presubiculum regions. Neuropsychological studies have largely supported these findings. Studies conducted to date have suggested in general greater neuropsychological impairment among delusional AD patients [19, 27–32], with more deficits in classic executive (frontal lobe) tasks [19, 31].

The question of whether or not delusions are associated with greater functional impairment has some very practical implications. Knowing this association would allow physicians and policy makers to develop interventions that would better target psychotic symptoms, leading to improved patient functional outcomes. The purpose of this review is to examine whether or not delusions are associated cross-sectionally with worse functional performance. We will attempt to do this by reviewing existing studies that have explored the relationship between real-world functioning and delusions. This will be followed by a discussion of possible explanations of our findings and their implications for future research.

Methods

Various medical databases, including Medline and Psychlit, were searched using the keywords: delusions, functional outcomes, activities of daily living, dementia and Alzheimer's disease. Studies were included in the review if they were available in English, involved patients with AD and delusions, and involved a minimum of 1 functional and 1 psychiatric scale. Studies that were longitudinal, did not distinguish delusions from hallucinations and included patients with other forms of dementia (such as Parkinson's disease, dementia with Lewy bodies, vascular dementia and frontal-temporal dementia) were excluded.

Results

Review of the literature yielded 6 citations that met the specified inclusion and exclusion criteria (table 1). Three of the studies were retrospective [35–37], and 3 were prospective in design [33, 34, 38]. The vast majority used the MMSE as the main cognitive measure while behavioural

and functional measures varied considerably across studies. Most of the studies used sample sizes averaging approximately 100 patients and were recruited from memory disorder clinics.

Discussion

Of the 6 studies meeting the specified inclusion and exclusion criteria [33–38], 3 showed a positive correlation between real-world functioning and the presence of delusions [34, 35, 38]. Two of the 3 studies which failed to show a positive correlation [36, 37] were retrospective in design, and this may have impacted on the results. Retrospective identification of delusions may be problematic, particularly if standardized scales are not used to detect the presence of delusions at the time the patients are assessed. Both patients and caregivers may be reluctant to volunteer this information unless specifically asked. Weiner et al. [37] studied autopsy-confirmed AD cases, but behavioural symptoms were arrived at through retrospective chart analysis, rather than through administration of discrete scales. As symptoms were not identified in any systematic way and the interpretation may have been variable, this may have confounded the results. Furthermore, the functional scale selected was the Clinical Dementia Rating Scale (CDR), a scale that looks less at specific IADL performance and more at global performance. Thus, subtle deficits in real-world functioning mediated by executive cognitive processing may not have been as apparent. The results obtained from the study by Mok et al. [36] are somewhat harder to explain. Clearly, the patient sample ($n = 100$) was adequate and behavioural symptoms were detected through administration of standardized scales. Two functional scales, the Barthel Index (measuring activities of daily living; ADL) and the Lawton's IADL score were used, covering the entire spectrum of daily functions. One would at least anticipate some correlation between the IADL scale and delusions, but this proved negative. The negative results of this study may again relate to the difficulty in accurately documenting the presence of delusions retrospectively. Notably, hallucinations again correlated well with overall functional performance as measured by the Barthel Index, and poorly with scales measuring more complex functions. Finally, the study by Green et al. [33] (although prospective in design, having an adequate sample size and using appropriate scales) failed to show a correlation, not only between delusions and functional ability, but also between behavioural symptoms in general and func-

tional ability. This study had some unique aspects which may have affected the results. First, single patient visits were used to establish the presence of behavioural symptoms. Thus, patients may have been identified as delusional without meeting any minimum time criterion. Second, other confounding factors, including use of psychotropic medication, were controlled for. As use of psychotropic medication may correlate with behavioural symptoms, this may have adversely affected the association.

Of the 3 studies showing a positive correlation, only 1 study [34] controlled for the confounding effects of impaired cognition. This is important as delusions have been shown in multiple studies to correlate with overall decline in cognitive functioning. Therefore, to prove it is in fact the presence of delusions and not the associated decline in cognition that is associated with impairment in daily function, it is important to control for the effects of impaired cognitive processing. The study of Harwood et al. [34] also showed an association between the presence of hallucinations and function as measured by the Blessed Dementia Scale (BDS). The BDS is a measure of function that looks at changes in everyday activities, such as spending money, basic habits (such as using the toilet) and changes in personality (such as coarsening of affect). It is possible that the Harwood et al. study [34], although showing a positive correlation between delusions and real-world functioning, may have actually underestimated the impact of delusions on real-world functioning given that the BDS does not address functions mediated by executive cognitive processing such as planning a shopping trip or preparing a meal. The study by Tekin et al. [35], although retrospective in design, did focus on IADL as opposed to ADL. This may partially explain the positive results, given the link to executive processing demands. The study by Liu et al. [38] was one of the few studies using the Barthel Index that showed a positive correlation between delusions and real-world functioning. It is hard to know how much this positive result could be related to discrepancies in overall cognitive processing.

One would anticipate, based on what we know about the correlation between delusions and executive cognitive processing, that functional measures which focus on these frontal lobe functions would be the most likely to show a difference. Only studies by Green et al. [33], Mok et al. [36] and Tekin et al. [35] used scales that focused on IADL performance (the Lawton IADL scale and the FAQ). However, only 1 of these studies showed a positive correlation [35]. Harwood et al. [34] used the BDS, a scale

that incorporates little measurement of executive cognitive processing. The positive results obtained in this study may in fact underestimate the true impact of delusions on real-world functioning. Both Weiner et al. [37] and Liu et al. [38] used fairly basic scales, including the Barthel and the CDR scale. However, only Liu's study [36] showed a positive correlation.

The majority of the studies looked at other behavioural symptoms, in addition to delusions, and the results are of interest. Green et al. [33] showed no correlation between the presence of behavioural symptoms and functional impairment. Mok et al. [36] found no correlation between behavioural symptoms, as measured by the NPI, and functional impairment. They did, however, show a relationship with hallucinations. Harwood et al. [34] found a correlation with both delusions and hallucinations, but not with other behavioural symptoms. Weiner et al. [37] found that all behavioural symptoms correlated, including delusions, as did Tekin et al. [35] and Liu [38]. Thus, it is not clear from the disparity of findings whether or not other behavioural symptoms are the major driving force behind the associated functional decline.

While most of the studies alluded to in this review were scientifically sound, some limitations should be pointed out. Many of the studies used very basic measures of functional performance (i.e. looking at basic functional tasks such as grooming, toileting) that did not incorporate those functions mediated by executive cognitive processing. These studies could have potentially underestimated the impact of delusions on functional performance. Furthermore, the studies varied in terms of their ability to deal with confounders linked to poor functional outcome such as age, socioeconomic status, medical comorbidity and, perhaps most importantly, cognitive impairment itself. Only the studies by Green et al. [33] and Harwood et al. [34] attempted to take into account the variance associated with cognition. In addition, the studies varied considerably in terms of how they defined a 'delusion'. Many of the studies sought caregiver input and used different rating scales. As delusions have been known to fluctuate considerably over time, it would be important for there to be a minimum time criterion from the onset of the delusion to time of testing. Finally, with the exception of the study by Green et al. [33], none of the studies alluded to the use of psychoactive medications, such as antipsychotic medications or cognitive enhancers, which may independently affect real-world functioning.

Conclusion

In conclusion, this review suggests that delusions may be associated with worse functional performance in patients with Alzheimer's disease. The full extent of the impact of delusions on functional performance in most studies performed to date may actually be underestimated. As demonstrated, most of the studies have relied on functional scales that emphasize basic tasks as opposed to more complex tasks. Furthermore, few of the studies attempted to account for the variance associated with cognition, and most used very basic measures of cognition which lacked sensitivity, possibly leading to inaccurate results. Specifically, none of the studies used measures of executive cognitive impairment which may have correlated well with the decline in function based on previous research. Data captured about the delusions was limited in terms of severity and duration. Finally, the studies examined in the course of this review were all cross-sectional in nature – no longitudinal studies were analyzed. Future studies could improve on these limitations by incorporating more detail about delusional severity, conducting more longitudinal studies, and using cognitive and functional measures that are better at detecting executive impairment.

Acknowledgements

The authors would like to gratefully acknowledge the Alzheimer society of Canada for their support.

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