

Psychosis in Alzheimer's disease: Prevalence, clinical characteristics, symptom co-morbidity, and aetiology



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Alzheimer's disease was identified almost a century ago. Cognitive morbidity (deterioration in memory, attention, language, and executive functioning) was regarded as a sufficient index for the description and diagnosis of Alzheimer's disease. Within the cognitive discourse, the importance of neuropsychiatric and neurobehavioural referents was often eschewed. Recent research studies attest to the profound impact of the non-cognitive symptoms on the quality of life of both patient and caregiver. The purpose of this article is to review studies on psychosis in Alzheimer's disease, examine its prevalence, and discuss its manifestation with reference to the association between neuropathology and psychotic disturbances. The importance of clarifying the validity of the construct 'psychosis in Alzheimer's disease', the specificity of symptoms, and the phenomenology of subtypes with their distinct clinical and biological associations is addressed.

Keywords: Alzheimer's disease; delusions; hallucinations; non-cognitive; psychosis

The most common dementia syndrome bears the name of its discoverer, Alois Alzheimer, who described it as an insidious, progressive, and perplexing condition (Alzheimer, 1977). The incidence of new cases of Alzheimer's disease increases exponentially with age; therefore one can predict an ever-burgeoning economic crisis in the health care system on the bases of an increasing lifespan and a fast-growing segment of the at-risk population (Charlton, 2003). In South Africa, for example, it is estimated that 3.7 million people are over the age of 60 years (7.7% of the population), and this figure is expected to increase in the future (Statistics South Africa, 2006).

In terms of the neuropathological and cognitive substrates, this disease is imbued with a relative uniformity that expedites classification and diagnosis. The non-cognitive manifestations, however, hint at an intricate network of psychological and biological antecedents and disease processes that may confound the occurrence of these manifestations. The latter conjecture is strengthened by illustration; studies indicated that neuropathology alone couldn't account for the heterogeneous non-cognitive profiles

observed in Alzheimer's disease patients (Cummings, 2005). This lack of established causality between neuropathology and symptom occurrence illuminates the need to understand the phenomenology of the non-cognitive symptoms that appear in the neuropsychological profile of an Alzheimer's patient. Non-cognitive is a term that can be used to describe a range of neurobehavioural signs (e.g., wandering, restlessness, sleep disturbances) and neuropsychiatric symptoms (e.g., depression, anxiety, psychosis) that manifest during the dementing process.

This article reviews literature on psychotic symptoms that manifest during the Alzheimer's disease process. A systematic search was conducted using the PubMed, EBSCO, and Science Direct databases using the keywords Alzheimer's disease, dementia, psychosis, delusions, and hallucinations. Articles relevant to the aim of this article were selected for review. For the purposes of this article, delusions and hallucinations will be discussed separately. This follows trends in current research, which indicate that delusions and hallucinations may be independent composites of the psychotic syndrome that manifests in Alzheimer's disease and thus warrant separate discussion of prevalence, risk factors, symptom co-morbidity, and aetiology. The aim of this article is to discuss the specificity (validity of the construct) and non-specificity (concomitant and by-product of underlying neuropathology) of psychosis in Alzheimer's disease and elucidate the specific clinical and biological associations of delusions and hallucinations.

The introductory section of the article highlights the concept of psychosis in Alzheimer's disease. The first section of this article includes a review of the prevalence, clinical characteristics, symptom co-morbidity, and aetiology of delusions and the second section includes a review of the prevalence, clinical characteristics, symptom co-morbidity, and aetiology of hallucinations. The final section entails a brief extrapolation of key issues pertaining to the studies reviewed and the relevance of these findings to the management of Alzheimer's disease.

PSYCHOSIS IN ALZHEIMER'S DISEASE

In his first description of Alzheimer's disease, Alois Alzheimer (1977) alluded to delusions and hallucinations experienced by his 51-year old patient. Since then, many studies have reported on the prevalence of psychotic episodes in Alzheimer's disease, and psychosis in Alzheimer's disease has predominately alluded to the occurrence of delusions and hallucinations (Sweet, Nimgaonkar, Devlin, & Jeste, 2003). Ropacki and Jeste (2005) suggest that the focus on delusions and hallucinations is the result of improvements in the development of diagnostic criteria and measurement scales dealing with these specific symptoms in Alzheimer's disease.

There is, however, little consensus about the prevalence of psychotic symptoms in Alzheimer's disease (Cummings, 2005). This is partly due to the difficulties experienced in diagnosing these symptoms in the context of dementia and distinguishing whether the symptoms are non-specific aspects of the underlying disease or a distinct phenotype

in Alzheimer's disease (Lind et al., 2006). According to Jeste, Blazer, and First (2005) the provisional criteria for diagnosis of psychosis in Alzheimer's disease include: (a) emergence of characteristic delusions and hallucinations in the presence of possible or probable Alzheimer's disease, (b) emergence of psychotic disturbances after onset of other dementia symptoms, (c) intermittent presence of symptoms for at least a month, (d) severity of psychotic symptoms disrupting functioning of patient and family, (e) identification of associated symptoms such as aggression and depression, and (f) not attributable to other co-morbid conditions such as delirium, medical condition, drug effects, and another psychotic disorder.

Using aspects of the classification criteria, several studies indicate prevalence estimates of psychosis from 10% to 84% with an average range of 28% to 38% (e.g., Cassimjee, Stuart, & Marchetti-Mercer, 2005; Lopez et al., 2000; Schreinzer et al., 2005; Srikanth, Nagaraja, & Ratnavalli, 2005). These studies have been conducted in South Africa, India, Europe, and the USA, using community and clinic samples that ranged from 44 to 145 Alzheimer's patients assessed on various non-cognitive rating scales (e.g., Neuropsychiatric Inventory (NPI), Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), CERAD Behaviour Rating Scale for Dementia). Studies reporting on the incidence of psychosis in Alzheimer's disease in the US population show that over 50% of patients with Alzheimer's disease would eventually manifest with psychotic disturbances and the incidence increases over the course of the disease (Lyketsos et al., 2000).

In a population-based study on 5 092 elderly people in Utah (USA), Lyketsos et al. (2000) compared the elderly with dementia to those without on the NPI rating scale. They found that the prevalence of psychotic symptoms was much higher in the participants with dementia in comparison with the participants without dementia. The higher prevalence of psychotic symptoms in the elderly with dementia suggests that neuropsychiatric disturbances that accompany Alzheimer's disease may warrant diagnosis and treatment as a specific disorder and not merely a reflection of cognitive impairment associated with aging. Mirakhor, Craig, Hart, McIlroy, and Passmore (2004) provide statistical validation for a psychosis syndrome in Alzheimer's disease. The researchers conducted a factor analysis on the NPI subscores of 435 patients with Alzheimer's disease and found evidence for four factors (affect, physical behaviours, hypomania, and psychosis). Delusions and hallucinations had the highest loading on the psychosis factor, and it remained consistent when different methods of statistical rotation were used.

The psychotic disturbances in Alzheimer's disease have clinical and social implications. On a clinical level, psychotic disturbances can diminish the patient's quality of life and compound cognitive impairment because of their psychological and neuropathological correlates. On a social level, the occurrence of delusions and hallucinations may increase caregiver burden, precipitate decisions to institutionalise patients, and impact on the quality of life of both caregiver and patient.

DELUSIONS IN ALZHEIMER'S DISEASE

Previous research by Cutting (1987) and Cummings (1992) has indicated that patients with organic diseases typically display five categories of delusional symptoms, namely simple persecutory, complex persecutory, grandiose, bizarre/multiple delusions, and delusions linked to an underlying neurological impairment (e.g., neglect syndrome & Anton's syndrome). In contrast to schizophrenia, however, recent research has shown that delusions in Alzheimer's disease are simple and typically paranoid or persecutory in nature (Fisher, Bozanovic-Sosic, & Norris, 2004; Lopez et al., 2000). Sweet et al. (2003) caution, however, that the persecutory and paranoid delusions may represent for the patient with Alzheimer's disease an accurate account of reality in the presence of a memory disorder, and the diagnosis of delusions can be clinically challenging in this regard. They emphasise that, in the presence of an organic memory disorder, the delusional ideas must be recurrent and persistent over time to exclude the possibility that the delusional ideas coincide with a memory dysfunction.

Several researchers concur that among patients with Alzheimer's disease simple persecutory delusions appear to be the most common. For example, Burns, Jacoby, and Levy (1990a) report delusions of theft and suspicion as most common among their sample. Similarly, Deutsch, Bylsma, Rovner, Steele, and Folstein (1991) found that 73% of delusions reported in their study warrant a classification of simple persecutory delusions (theft, suspiciousness, abandonment, and threat of harm) and Chen, Borson, and Scanlan (2000) found that 72% of their cohort had simple paranoid delusions. Although simple delusions are considered typical in Alzheimer's disease, Schneider and Dagerman (2004) caution that the two commonly used standardised rating scales are designed to elicit these specific types of delusion. Therefore, the range of symptomatology may not be adequately captured because of the limitations of the structured rating scales.

Prevalence of delusions in Alzheimer's disease

Delusions and hallucinations often co-occur, and in the majority of studies a higher frequency of delusions compared to hallucinations was observed in both clinical and community populations and cross-sectional and longitudinal studies (Assal & Cummings, 2002; Bassiony et al., 2000; Bylsma et al., 1994; Drevets & Rubin, 1989; Jeste, Wragg, Salmon, Harris, & Thal, 1992; Jost & Grosssberg, 1996; Kotrla, Chacko, Harper, & Doody, 1995; Lopez et al., 1996; Lyketsos et al., 1997; Nambudiri, Teusik, Fensterheim, & Young, 1997; Reisberg et al., 1987; Ropacki & Jeste, 2005).

Prevalence estimates for delusions in Alzheimer's disease range from 10% to 75%, with a prevalence average of one-third of patients manifesting with delusions (Baiyewu et al., 2003; Lyketsos et al., 2001; Trabucchi & Bianchetti, 1996). The use of inconsistent definitions of delusions and hallucinations, methods of diagnosis, and different population sources accounts for the variance in estimates.

Delusions and clinical characteristics

Delusions have been associated with a number of clinical characteristics. Significant relationships are noted for delusions and the severity of cognitive impairment (Aalten, De Vugt, Jaspers, Jolles, & Verhey, 2005; Baiyewu et al., 2003; Doody, Massman, Mahurin, & Law, 1995; Paulsen, Ready et al., 2000), functional impairment (Binetti et al., 1995; Drevets & Rubin, 1989; Galasko, Gould, Abramson, & Salmon, 2000), severity of disease (Piccininni, Di Carlo, Baldereschi, Zaccara, & Inzitari, 2005; Trabucchi & Bianchetti, 1996), age (Bassiony et al., 2000), and female gender (Leroi, Voulgari, Breitner, & Lyketsos, 2003).

The association reported between delusions and rate of cognitive decline is contentious because the results of several studies are inconclusive and contradictory. Many of these studies have grouped delusions and hallucinations under the rubric of psychosis and found that psychosis in Alzheimer's disease is significantly associated with more rapid cognitive decline (Chui, Lyness, Sobel, & Schneider, 1994; Drevets & Rubin, 1989; Harwood, Barker, Ownby, & Duara, 2000; Paulsen, Salmon et al., 2000). Sweet et al. (2003) note that some of these studies did not control for duration of illness and this may have confounded some of the results.

Paulsen, Ready, et al. (2000) state that their results indicate that rapid cognitive decline and psychosis may not be independent of each other, but it is unclear if the rapid impairment precedes, follows, or coincides with psychosis onset. Studies that indicate no relationships between rapid cognitive decline and psychosis onset have tended to distinguish the psychosis symptoms very specifically. For example, Bylsma et al. (1994) report no association between delusions and cognitive decline. Their findings are attributable to the distinct manner in which symptoms were defined, and the separation of patients with Alzheimer's disease into a group with a primary delusion and a group with delusions secondary to hallucinations or affective disorders.

Corroborating these earlier findings, Perez-Madrinan et al. (2004) suggest that a separate analysis of the subtypes of psychotic symptoms in Alzheimer's disease may yield different results. In their comparative study, they distinguished between a paranoid subtype (delusion) and a misidentification subtype (hallucinations), compared the cognitive performance between these groups, and compared cognitive performance of both groups with patients with Alzheimer's disease without psychosis. After controlling for duration of illness, age, and education level, they found that the group classified as the paranoid subtype did not differ in cognitive performance from the non-psychotic group, but the group classified as the hallucination subtype was significantly more cognitively impaired than the non-psychotic group. Current research provides evidence for psychosis subtypes in Alzheimer's disease and attests to the importance of delineating the syndromal concept of psychosis in Alzheimer's disease into its composites, which may yield meaningful clinical and biologic data (Fischer et al., 2006; Wilkosz, Miyahara, Lopez, DeKosky, & Sweet (2006).

According to Trabucchi and Bianchetti (1996), the prevalence of delusions remains consistent across mild, moderate, and advanced stages of the disease. However, some researchers found delusions to be most common in the moderate stage of Alzheimer's disease (Aalten et al., 2005; Lyketsos et al., 2000), and others show that the prevalence is higher in the advanced stages (Leroi et al., 2003; Piccininni et al., 2005). Schneider and Dagerman (2004) contend that current research shows that the symptoms of psychosis persist over time and can occur at various stages of the disease. According to Lyketsos et al. (2001) and Paulsen, Salmon, et al. (2000), incidence of onset of delusions among patients who had no symptomatology at initial evaluation was 20% to 27% at one year, 36% at two years, and 50% at three years, and the symptoms were persistent for a period of three months to one year (Schneider, Katz, Park, Azen, & Martinez, 2003; Schneider & Kershaw, 2001). Within the spectrum of non-cognitive symptoms, some researchers have found that delusions are the least persistent among the neuropsychiatric symptoms but are still associated with caregiver distress, and the presence of delusions is a significant predictor of patient institutionalisation (Baiyewu et al., 2003; Craig, Mirakhur, McIlroy, & Passmore, 2005).

With regard to age, age at onset of disease, duration of disease, and education level, studies report equivocal results and weak correlations between delusional symptoms and these characteristics (Ropacki & Jeste, 2005; Sultzer et al., 2003).

Delusions and symptom co-morbidity

Delusions share significant associations with other behavioural symptoms. Alzheimer's patients with delusions exhibit aggressive behaviours and severe activity disturbances when compared to Alzheimer's patients without delusions (Bassiony et al., 2000; Flynn, Cummings, & Gornbein, 1991). Mixed results were found for the increased presence of extrapyramidal signs in Alzheimer's disease groups with psychotic disturbances (Jeste et al., 1992; Stern, Mayeux, Sano, Hauser, & Busht, 1987). Sweet et al. (1998) report that extrapyramidal symptoms are linked to Alzheimer's disease independent of any psychotic or affective co-morbidity, whereas Caligiuri and Peavy (2000) show an association between parkinsonism and psychosis, and severity of neurobehaviours and parkinsonism. Paulsen, Salmon et al. (2000) found that extrapyramidal symptoms such as rigidity, unstable posture, and gait abnormalities predate the onset of psychosis in their cohort and indicate that extrapyramidal symptoms may serve as a risk factor for psychosis onset. This latter association makes neurological sense because similar neuropathological processes (hypofrontality and neurochemical imbalances) are implicated in psychosis and extrapyramidal dysfunction (Hermann, Lanctôt, & Khan, 2004; Lopez et al., 2000). The researchers, however, caution that the extrapyramidal symptoms may be side effects of prescribed neuroleptics used for the treatment of delusions, and studies that do not control for this may confound the relationship between these variables.

In an earlier study, Deutsch et al. (1991) found that acts of aggression and a delusional episode were reported to have co-occurred in approximately 90% of the cases they

reviewed. Most of these aggressive episodes happened during an interpersonal situation with a caregiver, suggesting that the social relationship with the caregiver contributes in a manner to these disturbances. In an investigation of patients with Alzheimer's disease and delusions, Sultzer et al. (2003) administered three standardised tests to determine cognitive performance (Mini-Mental State Examination), depression (Hamilton Depression Scale), and neuropsychiatric and neurobehavioural symptoms (Neurobehavioural Rating Scale). They found that within the sample of patients with Alzheimer's disease and delusions there was a significant correlation between the severity of delusions and the agitation factor score. In a subsequent study, Mizrahi, Starkstein, Jorge, and Robinson (2006) found that the presence of delusions was significantly and independently correlated with the neuropsychiatric features of depression and anosognosia, and the neurobehavioural symptoms of aggression and agitation. Evidence from genetic studies indicates that the association between aggression and delusions may be attributable to a genetic polymorphism, which contributes to an associated phenotype for psychotic and aggressive symptoms (Sweet et al., 2003).

Bylsma et al. (1994) and Bassiony et al. (2002) report an association between disturbance of personality and mood in groups of Alzheimer's patients with delusions. Bassiony et al. (2002) compared 75 community-dwelling patients with probable Alzheimer's disease and delusions to a control group of 228 patients with probable Alzheimer's disease and no delusions. The patients were administered the Cornell Scale for Depression in Dementia (CSDD), Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR), Psychogeriatric Dependency Rating Scale (PGDRS-P), and the General Medical Health Rating (GMHR). After adjustment for confounding variables (e.g., gender, age, marital status, education level, functional ability, cognitive performance) multiple logistic regression analysis yielded a significant association between delusions and depression and no other significant associations between delusions and other variables. In an earlier study, Drevets and Rubin (1989) suggest that, in addition to the different underlying neuropathology, patients with psychotic disturbances appear to have a lower mortality level than non-psychotic patients, and they attribute this to patients with Alzheimer's disease and psychosis receiving a different quality of care, which may have a positive psychological impact and contribute to their longevity. In a longitudinal study spanning 14 years, Scarmeas et al. (2005) provide corroborating evidence for the association between delusions and mortality. In their longitudinal comparative study, results show that the presence of delusions was a time-dependent predictor of cognitive and functional decline but not mortality.

Aetiology of delusions

Neuroimaging and electroencephalographic studies have shown that there are structural and functional differences in Alzheimer's disease patients with and without psychosis (Faber et al., 2000; Zubenko, Moosy, Martinez, Rao, & Claasen, 1991). Psychotic disturbances

have been associated with a higher density of plaques and tangles in the neocortex and imbalances in levels of norepinephrine, serotonin, and dopamine in the cortex and subcortex (Herrmann et al., 2004; Minger et al., 2000; Zubenko et al., 1991). However, Sweet et al. (2003) found no significant association between neurofibrillary tangles in six brain regions in a matched Alzheimer's disease group with and without psychosis. The equivocal results can be attributed to undiagnosed comorbid conditions (e.g., Lewy body dementia) that may accompany the disease and the possibility that only some cases of psychosis in Alzheimer's disease may result from tangles and plaques.

Evidence from the few neuropsychological studies on patient groups with and without psychosis indicates that the patients with Alzheimer's disease and psychosis have greater performance deficits on tests of frontal lobe functioning (Sultzer et al., 2003). In an earlier study, Jeste et al. (1992) compare the neuropsychological performance of patients with Alzheimer's disease and delusions with the performance of those patients with Alzheimer's disease and no delusions. They report that the patients with delusions performed poorly on the tests of verbal fluency. The authors relate this to a semantic memory deficit and conclude that delusional patients show a disruption in the semantic memory circuits and, by association, fronto-temporal dysfunction. In a recent study, Perez-Madrinan et al. (2004) differentiated the Alzheimer's patients with psychosis into two groups, the first characterised by misidentifications and hallucinations, and the second by persecutory delusions. They compared the two groups' performance on neuropsychological measures, and compared the two groups' performance with a group of patients with Alzheimer's disease without psychosis. They found that the group with paranoid delusions showed no significant difference in test performance from the non-psychotic group, whereas the group with misidentifications and hallucinations performed significantly lower on tests of verbal fluency and visuospatial ability. They concluded that the two groups were distinct subtypes of Alzheimer's disease, and that the paranoid phenotype may have different underlying neuropathology from other subtypes of psychosis.

Support for the involvement of fronto-temporal areas comes from neuropathological studies. Lopez, Smith, Becker, Cidis-Meltzer, and DeKosky (2001) investigated the neuropathological mechanisms underlying psychosis in Alzheimer's disease using Positron Emission Tomography. They concluded that patients with psychosis have significantly lower relative cerebral blood flow in fronto-temporal regions relative to patients without psychotic symptoms. In an investigation of the role of the cholinergic system in the manifestation of psychosis in Alzheimer's disease, Lai et al. (2001) found that specific muscarinic receptor density is significantly augmented in the frontal cortex of Alzheimer's patients with delusions.

Sultzer et al. (2003), using Positron Emission Tomography to determine glucose metabolism in the brain regions of Alzheimer's disease patients with delusions, affirmed the earlier results. After applying linear regression modelling and controlling for cognitive deficits, they reported that patients with Alzheimer's disease and delusions have hypometabolism in two areas of the right prefrontal cortex. The data from numerous

studies suggest that the symptoms of psychosis and particularly delusions appear to have a significant association with the functioning of the fronto-temporal areas and the accompanying neurochemical correlates (Lai et al., 2001), while other research studies provide evidence to the contrary (Minger et al., 2000; Van Hoesen, Parvizi, & Chu, 2000). Some of the equivocal findings can be attributed to the use of an inconsistent definition of psychosis/delusions, different patient samples (disease staging), use of global (MMSE) and specific measures of cognitive status (neuropsychological tests), and different measures of non-cognitive symptoms.

Some researchers suggest that, in addition to fronto-temporal involvement, temporo-parietal cortical lesions may disrupt information flow to the limbic system causing disharmonious information channelling, and this may result in delusional and hallucinatory episodes (Lopez et al., 1996; Mega et al., 2000). For example, hypoperfusion in the temporal lobes of patients with Alzheimer's disease has also been found in a comparative study between groups with and without delusions (Starkstein et al., 1994). Sultzer et al. (2003) argue that most studies indicate that frontal dysfunction is central to the manifestation of psychoses in general and delusions specifically. They hypothesise that the findings suggest that different areas of the brain may subservise specific types of delusion, and studies often report on the presence or absence of delusions but rarely distinguish or ascertain the nature of the delusional thoughts.

Earlier studies have indicated that a relatively intact cortex and cognitive integrity is needed for psychotic disturbances to occur and the complexity of the delusions is determined by the intactness of the brain (Cummings, 1992). Burns, Jacoby, and Levy (1990b) and Förstl, Burns, Levy, and Cairns (1994), for example, found that Alzheimer's patients with delusions have less brain atrophy and ventricular augmentation than non-delusional Alzheimer's disease groups. Subgroups of patients with delusions had higher neuronal counts in the hippocampal structures when compared to non-delusional Alzheimer's disease patients. The high prevalence of delusions in the moderate stages and an attenuation of symptoms in the advanced stages suggest that a relative threshold of cognitive integrity is required for the delusions to occur (Lyketsos et al., 2000; Ropacki & Jeste, 2005). Taken together, these studies propose that delusions are more likely to occur in the early stages of the disease, they may become less complex as the disease progresses, and different levels of cognitive integrity may underlie different delusional manifestations.

Staff et al. (2000) found that content-specific delusions were related to hypoperfusion in the right prefrontal cortex. Hirono et al. (1998) and Lopez et al. (1996) found that, in their samples of Alzheimer's patients with paranoid delusions, the temporal, orbito-frontal, and fronto-limbic cortex display abnormalities. In a more recent review of delusions in Alzheimer's disease, Blackwood, Harwood, Bentall, and Murray (2001) agree that frontal and temporal abnormalities underlie paranoid/persecutory delusions. A distributed collaborative cognitive network subserves these types of delusion, and the disruption of several cognitive processes contributes to their occurrence in Alzheimer's disease.

The subcallosal gyri, cingulate gyri, parahippocampal gyri, hippocampus, insular, and orbito-frontal region are the cortical representatives of the limbic system. These areas mediate the evaluation of environmental threat and danger, and fearful and anxious responses; thus disruption in the information flow in these pathways may underlie psychotic symptoms. Lai et al. (2001) suggest that temporal and orbito-frontal abnormalities may contribute to delusions of a persecutory and fearful nature because of the cortical region's association with the limbic system, whereas delusions that have a more content/factual nature are associated more with executive functions (e.g., volition, planning, self-regulation, purposive actions) and thus frontal dysfunction.

Summary

Taken together, the results of several studies have shown that delusions are common in Alzheimer's disease, are likely to occur in the moderate stages, have weak correlations with demographic variables such as age and illness duration, co-occur with depression, and aggression, and have a variable influence on the rate of cognitive deterioration.

Of interest in a disease characterised by progressive cognitive decline and hippocampal deterioration is the involvement of the frontal lobes in psychosis. Förstl et al. (1994) conclude that patients require some atrophy to initiate the psychotic episodes but have to be moderately capable intellectually in order to elaborate on the content of these. The frontal lobes are implicated in the expression of metacognitive skills that result in a theory of mind (Stuss, Gallup, & Alexander, 2001). Studies have shown that impaired executive monitoring in dementia patients (frontal activation) disrupts abilities of self-awareness, self-analysis, and reality awareness (Blackwood et al., 2001). With evidence of frontal atrophy in patients with Alzheimer's disease and delusions, problems of perspectivity in a spatial sense and a disruption in general self-monitoring capacity, and by inference a disturbed self-construct, are expected.

The evolution, pathogenesis, and expression of non-cognitive symptoms arise from a complex interplay of social, psychological, and biological characteristics. For example, research evidence shows that frontal atrophy reflects the biological association, disruptions in metacognitive abilities and premorbid antecedents (e.g., personality traits) reflect the psychological association, and caregiver characteristics and management strategies reflect the social associations for the variability in occurrence of symptoms (Aalten, Verhey, & Korten, 2001; Riello, Geroldi, Zanetti, & Frisoni, 2002; Sultzer et al., 2003). This multidimensional understanding of the aetiology of delusions in Alzheimer's disease allows for the use of both pharmacological and psychological interventions for the management and treatment of psychotic symptoms.

HALLUCINATIONS IN ALZHEIMER'S DISEASE

Hallucinations of a visual nature are common in Alzheimer's disease (Schneider &

Dagerman, 2004). These neuropsychiatric symptoms accompany other behavioural problems such as anxiety, agitation, and aggressiveness (Lopez et al., 1991; Wilkosz et al., 2006), influence the severity and frequency at which these occur (Kotrla et al., 1995; Mok, Chu, Chung, Chan, & Hui, 2004), and are associated with behaviours of frontal dysfunction (Paulsen, Ready et al., 2000).

Prevalence of hallucinations

According to a review of 55 studies ($n = 9\,749$) on the non-cognitive sequelae in Alzheimer's disease, Ropacki and Jeste (2005) found that hallucinations were prevalent in approximately 18% of the total sample. Several researchers report prevalence estimates from 3% to 50% (Chen et al., 2000; Lyketsos et al., 2001; Whitehouse et al., 1996) and indicate that hallucinations occur less frequently than delusions (Lyketsos et al., 2000; Srikanth et al., 2005). Prevalence estimates traverse a wide range as these estimates depend on the classification criteria that researchers endorse in their studies. Patients with Alzheimer's disease may have acute expressive language difficulties, and diagnosing the occurrence of hallucinations may be confounded by this neuropsychological deficit (Sweet et al., 2003).

Hallucinations and clinical characteristics

Impact and prevalence studies usually group delusions and hallucinations together; however, evidence points to different correlates for these symptoms. Burns et al. (1990a, 1990b) found that hallucinations influence the rate of cognitive decline but delusions have no significant effect on cognition. In a more recent study by Wilson, Gilley, Bennett, Beckett, and Evans (2000), results confirm that hallucinations have a more significant relationship with rate of cognitive decline than delusions. A cohort of 410 patients with Alzheimer's disease was assessed over a period of four years on neuropsychological measures of memory, visuoconstruction, repetition, and naming. The researchers report that the patients with Alzheimer's disease and hallucinations had lower baseline scores and a more rapid decline on these measures over four years when compared to the patients with Alzheimer's disease and delusions.

The different correlates associated with delusions and hallucinations lend credence to the subtype hypothesis, which states that hallucinations and delusions are distinct phenotypes of psychosis in Alzheimer's disease (Piccininni et al., 2005; Trabucchi & Bianchetti, 1996). Expanding on the idea of subtypes, Leroi et al. (2003), using data from a US-based epidemiological study, examined the phenomenology of psychiatric symptoms in Alzheimer's disease. They found that delusions have significant associations with demographic and clinical variables, whereas the occurrence of hallucinations in Alzheimer's disease seems to be unrelated to clinical and demographic correlates. In an earlier comparative study, Bassiony et al. (2000) investigated the prevalence of delusions and hallucinations, and the characteristics that correlated with each of these

symptoms. Hallucinations correlated negatively with education levels and positively with severity of dementia and duration of illness, whereas delusions correlated positively with age, depression, and aggression, and negatively with general health. The presence of hallucinations has also been negatively associated with functional outcomes (Mok et al., 2004), institutionalisation, and mortality (Scarmeas et al., 2005). The authors conclude that the phenomenon of psychosis in Alzheimer's disease is a composite of distinct subtypes that may have different underlying clinical, demographic, and neuropathological substrates.

Further evidence for the subtype hypothesis comes from statistical analysis undertaken in studies on psychosis in Alzheimer's disease. Cook et al. (2003) conducted a factor and cluster analysis on items related to psychotic symptoms on the CERAD Behaviour Rating Scale for Dementia. They identified two distinct subtypes of psychosis, namely misidentification/hallucinations and persecutory delusions. Corroborating evidence for distinct subtypes was further sourced from a recent study, which identified for the first time symptom clusters on the BEHAVE-AD using component factor analysis on subscores (Schreinzer et al., 2005). The researchers identified three factors, namely agitation disturbances, affectivity disturbances, and diurnal rhythm disturbances. Hallucinations show the highest factor loading (0.75) on diurnal rhythm disturbances, and delusions show the highest factor loading on agitation disturbances (0.53). These results further corroborate the hypothesis that delusions and hallucinations may have different underlying substrates and aetiologies.

Hallucinations and symptom co-morbidity

In the first 15 reported cases of Alzheimer's disease, delusions and hallucinations co-occurred in 80% of the patients (Berrios, 1990). Several other symptoms such as parkinsonian gait, bradyphrenia, poor semantic memory, and aberrant motor activities were also associated with occurrence of hallucinations in patients with Alzheimer's disease (Paulsen, Salmon, et al., 2000). With regard to the co-occurrence of other non-cognitive symptoms, Rapoport et al. (2001) found that aggression and apathy are significantly associated with the presence of hallucinations, and Mok et al. (2004) report that hallucinations have a positive correlation with the occurrence of symptoms of disinhibition and anxiety.

Taken together, the results of research suggest that hallucinations tend to occur sporadically, seem to be more prevalent in the advanced stages of the disease, and co-occur with symptoms of aggression and anxiety. Thus, recognition of the specificity of the symptoms and their biologic and psychological associations will contribute to efficacious management of symptoms and may attenuate the occurrence of co-morbid conditions, hence alleviating some of the suffering for the patient and caregiver.

Aetiology of hallucinations

Psychosis in Alzheimer's disease has been linked to the functioning of the cholinergic system (Cummings & Kaufer, 1996; Frölich, 2002). In an investigation of specific muscarinic receptors, Lai et al. (2001) found that alterations in the M¹ and M² muscarinic receptors may underlie the occurrence of hallucinations and delusions in Alzheimer's disease. Hallucinations were positively correlated with M² receptor density in the temporal lobe region. The temporal region is involved in sensory processing, and an alteration in this area appears to coincide with the occurrence of hallucinations. The M² receptors are classified as postsynaptic autoreceptors that inhibit the release of acetylcholine (Teaktong et al., 2005). The paradoxical effect whereby drugs which are muscarine antagonists induce hallucinations in the users suggests that cortical acetylcholine may be involved in processes of consciousness, and symptoms such as hallucinations may be derivatives of the perturbations in conscious processing of information (Frölich, 2002; Perry & Perry, 1995).

Previous research on acetylcholine and frontal lobe functioning has focused mainly on mnemonic functions and the role of acetylcholine in learning (Hasselmo, 2005). In order to fathom the role of acetylcholine in the pathogenesis of hallucinations, researchers have suggested that, in the context of an organic brain disease, the dual nature of consciousness must be understood (Perry & Perry, 1995, 2004). According to these researchers, the focus should be broadened to include the role of acetylcholine in the processing of input; that is, extrinsic analysis versus the analysis of information based on prior learning (intrinsic). The dual definitions of consciousness pertain to interacting networks of arousal and content. The former 'which is analogous in mechanistic terms to volume control' defines the force of overall neural stimulation, whereas the latter 'which is analogous ... to channel selection' incorporates a unitary wave of present awareness (Perry & Perry, 1995, p. 241).

Normal cholinergic functioning enhances neural stimulation and allows for a distinction between specific neural firing and 'cortical clatter'. In other words, it maintains the signal to noise ratio. This ratio functions as a mediatory process on activity dynamics and augments the organism's responsiveness to external sensory stimuli relative to internal background noise. Disruption of this circuitry can produce hallucinations because of the inefficiency of this circuit in diminishing internal brain activity during perception. Thus, 'cortical clatter' is augmented and there is a disruption in the streams of consciousness because of the increased noise to signal ratio. Moreover, disruption of cholinergic functions may cause an unusual dominance of sensory input interpretations based on prior representations (top-down activity).

The dominance of top-down or noise processing causes a detour in information flow away from the cortical representations, which act as matching processes with bottom-up sensory input. Thus, the flow of environmental input eludes evaluation against the internally retrieved information (top-down) resulting in a diminished interpretative

capacity to handle sensory information (Hasselmo & McGaughy, 2004). In this manner, alterations in acetylcholine levels disrupt the streams of conscious processing and may be a causative factor underlying the manifestation of hallucinations in Alzheimer's disease.

Summary

Taken together, results of studies on hallucinations indicate that they are prevalent in the advanced stages of the disease, significantly correlate with rapid cognitive decline, co-occur with aggression and aberrant motor behaviour, and may arise from disruptions in the cholinergic system.

Three factors caution against explanations that focus on a single biological cause. First, hallucinations most often occur with other specific behavioural symptoms suggesting involvement of a complex network of neuropathological, neurochemical, and psychosocial factors. Second, hallucinations have a complex neuroanatomic relationship with cognitive performance and the association between hallucinations and severity of cognitive impairment and rapid cognitive decline hints at a shared neuropathological and psychological mechanism (Sweet et al., 2003). Third, there is a discrepancy between clinical experience and pathophysiology, which underlies the cholinergic hypothesis in Alzheimer's disease. Studies found that the cholinergic deficits occur later in the disease and up-regulation or compensatory responses in the cholinergic system occur in the early stages of the disease (Frölich, 2002). These factors indicate that the use of cholinergic drugs in the mild stages of the disease may not provide significant clinical benefits and may cause unwanted side effects, and alternative treatment strategies including psychological intervention may be more beneficial in the mild stages of the disease.

CONCLUSION

A review of the literature on psychosis in Alzheimer's disease suggests that: (a) these symptoms are common in the evolution of the disease, (b) the nature of psychotic symptoms (content of delusions and hallucinations) is different from that of schizophrenia and other diseases (e.g., Lewy Body dementia), (c) there is a specificity and persistence of symptoms, and (d) patients with psychotic symptoms differ clinically, demographically, and neuropathologically from those without psychotic symptoms.

These factors inform the hypothesis that psychosis in Alzheimer's disease is not merely an epiphenomenon of advanced Alzheimer's disease, represents a clinical and biologically specific process, and affirms the validity of the construct of psychosis in Alzheimer's disease (Schneider & Dagerman, 2004; Sweet et al., 2003).

Recent research indicates that hallucinations and delusions are distinct phenotypes and composites that reflect the syndromal concept known as psychosis in Alzheimer's disease. The importance of recognising these subtypes in Alzheimer's disease is subserved by studies which indicate that the subtypes have different associations to clinical characteristics,

symptom co-morbidity, and aetiology. Moreover, factors unique to each subtype may influence the extent, frequency, content, and timing of psychotic symptoms. Neurobehavioural and neuropsychiatric symptoms in Alzheimer's disease are not a unitary concept, and the development of specific instruments for specific behaviours attests to the recognition of this in current research. To date, there are specific instruments that measure depression, agitation, and apathy in Alzheimer's disease. However, specific standardised measures for delusions and hallucinations in Alzheimer's disease are lacking (Robert et al., 2005).

RECOMMENDATIONS

Future studies should explore the development of specific measures and the distinct associations of subtypes. Research focused in this manner may yield interesting biologic and clinical associations that will help in the design of more efficacious clinical interventions and facilitate caregiver management of distinct psychotic symptoms in Alzheimer's disease. These strategies in turn will help improve the quality of life of both patient and caregiver and reduce the burden of care and its accompanying psychological morbidity. Irrespective of the debate over the absence (non-specific symptom of underlying disease) or presence (specific to a psychotic disorder) of syndromic psychosis in Alzheimer's disease, the impact on quality of care and quality of life is tangible.

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