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Neurobehaviors and psychotic symptoms in Alzheimer's disease

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Abstract

Psychotic symptoms are common in Alzheimer's disease (AD) and clinicoanatomical and neuropsychological evidence indicate an association between these symptoms and frontal lobe dysfunction. Neurobehaviors associated with frontal dysfunction were assessed in Alzheimer's disease (AD) patients with ($n = 20$) and without psychotic symptoms ($n = 21$) matched for mean age, education, gender, and dementia severity. The Frontal Lobe Personality Scale (FLOPs) was completed by patient caregivers to measure behaviors typically associated with frontal dysfunction. Findings indicated that AD patients with psychotic symptoms exhibited significantly greater neurobehavioral dysfunction (FLOPs $M = 130.69$, $SD = 24.70$) than AD patients without psychotic symptoms (FLOPs $M = 111.10$, $SD = 25.83$). Subscale analyses indicated that psychotic AD patients were more disinhibited ($M = 28.28$, $SD = 7.54$) than patients without psychotic symptoms ($M = 20.92$, $SD = 4.9$). Findings are consistent with and contribute to previous neuropsychological and clinicoanatomical research suggesting increased frontal dysfunction in AD with psychotic symptoms and lend additional empirical support to subtyping AD based on the presence of psychotic symptoms. Furthermore, findings provide preliminary evidence indicating which specific type of neurobehavioral abnormalities are related to the presence of distressing psychotic symptoms. (*JINS*, 2000, *6*, 815–820.)

Keywords: Dementia, Psychosis, Alzheimer's disease, Neurobehavioral syndromes

INTRODUCTION

Prevalence rates of psychotic symptoms in Alzheimer's disease (AD) range from 10% (Birkett, 1972) to 73% (Leuchter & Spar, 1985), with rates in clinical populations exceeding community-based samples (Rao & Lyketsos, 1998). Psychotic symptoms have implications for the management, treatment, course, prognosis, and pathophysiology of AD. Specifically, psychotic symptoms are chronic (Rosen & Zubenko, 1991) and are associated with longer duration of illness (Hirono et al., 1998) and more rapid progression of clinical course (Förstl et al., 1993; Lopez et al., 1991; Rosen & Zubenko, 1991; Stern et al., 1994). Indicators of specific neurological dysfunction such as extrapyramidal signs (Mayeux et al., 1985) and abnormal EEGs (Lopez et al., 1991) have been linked to psychotic symptoms in AD. Personality and behavioral changes including increased aggression (Deutsch et al., 1991; Flynn et al., 1991; Lopez et al., 1991), asocial behavior (Kotrla et al., 1995), and functional impairment (Stern et al., 1994) are associated with psychotic symptoms in AD and initial evidence suggests a link to premorbid personality traits of hostility and disagreeableness (Chatterjee et al., 1992). These findings have contributed to diagnostic subtyping of AD based on the presence of delusions (American Psychiatric Association (APA), 1994).

Evidence from neuropsychological investigations suggest relatively more executive dysfunction and findings from clinicoanatomical studies implicate increased frontal dysfunction in AD with psychotic symptoms than AD without these symptoms (Cummings & Kaufer, 1996; Flynn et al., 1991; Jeste et al., 1992; Rao & Lyketsos, 1998). For example, as compared to AD patients without psychotic symp-

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toms, neuropsychological studies indicated that AD patients with delusions were more impaired on an abstraction task (Flynn et al., 1991) and were more perseverative (Jeste et al., 1992). Using survival analyses we recently found that lower scores on measures of fluency, grooved pegboard, trail making, and digit span were predictors ($p < .05$) of future psychosis in AD (Paulsen et al., 2000). In addition, greater worsening on the DRS Attention and Construction subscales, total DRS, and fluency scores were associated with a two- to three-fold increase in the risk of developing psychosis. For instance, for every 1 *z*-score change in fluency, the risk of psychosis increased threefold.

In a review of several clinicoanatomical investigations, Cummings and Kaufer (1996) reported that psychotic symptoms were most strongly correlated with metabolic and perfusion abnormalities in frontal and temporal cortical regions. Rao and Lyketsos (1998) also noted that histological findings from autopsy studies and results of computed tomography (CT), electroencephalographic (EEG), and single-proton emission computed tomography (SPECT) studies converge to implicate distinct limbic system dysfunction in AD with psychotic symptoms. For example, in a study using positron emission tomography (PET) measures of cerebral metabolism, Sultzer (1996) reported correlations between severity of delusions in AD and reduced metabolic rate in four regions of the frontal cortex, including the anterior cingulate gyrus, the dorsal and medial prefrontal cortex, and the inferior frontal pole.

Based on these data indicating an association between psychotic symptoms in AD and executive and frontal dysfunction, we hypothesized that neurobehaviors associated with frontal dysfunction would be prevalent in AD with psychotic symptoms and greater than in patients without psychotic symptoms. Behavioral dysfunction in AD is important to study because of associations with caregivers' distress (Bedard et al., 1997; Kaufer et al., 1998; Rabins et al., 1982), premature institutionalization (Chenier, 1997; Chenowith & Spencer, 1986; Lieberman & Kramer, 1991; Steele et al., 1990), and increased need for care and supervision (Royall et al., 1993).

There are some limitations with existing neuropsychological research of behaviors indicative of frontal dysfunction in psychotic AD patients. First, dementia severity was not considered when assessing associations between psychosis and neuropsychological measures. Second, interpretation of findings is confounded and it is unclear if increased behavioral dysfunction is associated with the presence of psychotic symptoms or is a function of dementia severity. Findings from Chen et al. (1998) highlight the importance of taking into account general cognitive decline. In their study, psychotic symptoms were found to be negatively correlated with verbal fluency and performance on a deductive reasoning task but the negative associations between psychotic symptoms and neuropsychological test performance were no longer significant when dementia severity was entered as a covariate. In order to avoid ambiguity in interpretation of findings in this study, neurobehavioral syndromes were assessed in AD patients with and without psychotic symptoms who were matched for mean level of dementia severity.

METHODS

Research Participants

Participants in the NIH-funded Alzheimer's Disease Research Center at the University of California San Diego comprised the sample. Participants were diagnosed as AD by two senior staff neurologists according to criteria for "primary degenerative dementia" in the *Diagnostic and Statistical Manual of Mental Disorders–III–R* (APA, 1987) and by the criteria for *probable Alzheimer's disease* developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann et al., 1984). Extensive medical, laboratory, and neuropsychological testing was performed to rule out other possible causes of dementia.

The determination of psychosis was based on the National Institute of Mental Health Diagnostic Interview Schedule (DIS; Robins et al., 1981) for the DSM–III (APA, 1980). Twenty-one AD participants without psychotic symptoms and 20 participants with psychotic symptoms were matched on mean age ($t = -.16$, $p = .87$), education ($t = .60$, $p = .55$), gender (Mann–Whitney $U = 102.00$, $p = .61$), and dementia severity (MMSE $t = .58$, $p = .56$; DRS $t = .26$, $p = .80$). Of the AD patients with psychosis, 94% had delusions and 35% had hallucinations. All caregivers completed the FLOPs at the visit when psychosis was determined. Patients without psychosis were only eligible for study inclusion when all other ADRC evaluations also endorsed the absence of psychosis. Dementia severity was measured with two cognitive screening instruments, the Mattis Dementia Rating Scale (MDRS; Mattis, 1976) and the Mini-Mental State Exam (MMSE; Folstein et al., 1975). *T* tests indicated no significant differences ($p > .50$) between groups on subscales of the DRS. Total DRS scores were normally distributed between 17 and 124, and study participants were, on average, severely demented. All patients and their caregivers signed consent forms approved by the University's Institutional Review Board for the use of human subjects in research.

Measures

As part of an annual evaluation, the diagnosis of AD with psychotic symptoms required agreement between two board-certified research psychiatrists (I.G. and D.J.) through independent assessment. For the purposes of diagnosing AD patients with psychotic symptoms, DIS procedures were modified to obtain behavioral data collection in a structured manner from a close family member (usually the spouse). The diagnosis of psychotic symptoms required the presence of prominent delusions (e.g., paranoia, belief that spouse is

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an imposter) and/or hallucinations (e.g., visual, auditory, olfactory; Task Force on DSM–IV, 1991). Particular care was taken to differentiate delusions (fixed and persistent false beliefs) from confabulations (fabrications in response to questions that cannot be answered because of memory loss) and hallucinations were distinguished from misperceptions. Patients were diagnosed as psychotic only if their false beliefs were fixed, persistent and held despite caregiver persuasion to the contrary or if they responded to hallucinations as if they were real. Psychotic symptoms secondary to delirium, drug toxicity, or other "organic" factors (other than dementia) were excluded on detailed review of history, neurologic exam, and medication regimen.

Caregivers of all participants were also asked to complete two questionnaires, the Frontal Lobe Personality Scale (FLOPs; Grace & Malloy, 1992) and the Physical Self Maintenance Scale (PSMS; Lawton & Brody, 1969). The FLOPs is a theoretically derived, 46-item standardized rating scale that was designed to measure three neurobehavioral syndromes (executive dysfunction, disinhibition/irritability, apathy/akinesia) hypothesized to be associated with frontal lobe dysfunction. Evidence suggests that the total FLOPs scale demonstrates construct validity (Grace et al., in press) and that the instrument is useful in characterizing personality changes associated with neurodegenerative disease (Paulsen et al., 1996). Consistent with previous findings (Grace et al., in press), the FLOPs total scale demonstrated adequate internal consistency reliability as measured by Cronbach's alpha (total scale $\alpha = .94$). FLOPs subscales also exhibited adequate internal consistency (apathy $\alpha = .88$; executive function $\alpha = .87$; disinhibition $\alpha = .83$). There is no overlap in item content between the DIS and FLOPs. The PSMS is a six-item, 5-point rating scale measuring self-care abilities of feeding, dressing, toileting, grooming, physical ambulation, and bathing. The sum of all PSMS items was used in analyses with higher scores reflecting greater functional impairment.

RESULTS

The nonparametric Mann–Whitney *U* test was used for primary hypothesis testing because the distribution of the FLOPs and PSMS scores were not normal. Consistent with prediction and previous findings, total FLOPs score was significantly ($p < .05$) greater for psychotic ($M = 130.69$, $SD = 24.7$) compared to never psychotic patients ($M = 111.10$, $SD = 25.83$), indicating that AD patients with psychotic symptoms exhibited significantly more neurobehaviors associated with frontal dysfunction than patients without psychotic symptoms. This difference was largely due to differences on the FLOPs disinhibition subscale ($p < .05$; AD with psychotic symptoms $M = 28.28$, $SD = 7.54$; AD without psychotic symptoms $M = 20.92$, $SD = 4.90$), although there was a trend ($p < .10$) for scores on the apathy scale to be significantly different (AD with psychotic symptoms $M = 44.40$, $SD = 8.94$; AD without psychotic symptoms $M = 37.81$, $SD = 12.47$; see Figure 1). PSMS mean scores for psychotic ($M = 7.41$, $SD = 1.66$) and never-psychotic patients ($M = 7.18$, $SD = 1.67$) were not significantly different (Table 1).

Item-level comparisons of FLOPs ratings for AD patients with and without psychotic symptoms were examined to explore differences between these groups. Due to the large number of mean comparisons, a significance level of .01 was selected to reduce the possibility of Type I error. Mean scores on six items (three disinhibition and three apathy) were significantly higher in AD patients with psychotic symptoms (Table 2).

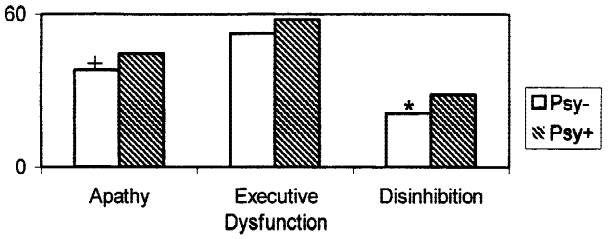

Fig. 1. FLOPs Subscale means for AD with (Psy+) and without (Psy−) psychotic symptoms. FLOPs = Frontal Lobe Personality Scale, AD = Alzheimer's disease. *Mean scores are significantly different ($p < .05$; Mann–Whitney *U* test). +Trend ($p < .10$; Mann–Whitney *U* test) for mean scores to be significantly different.

Table 1. Demographic and functional descriptives for Alzheimer's patients with and without psychotic symptoms

	AD without psychotic symptoms ($n = 21$)			AD with psychotic symptoms ($n = 20$)		
Measure	*M*	*SD*	Range	*M*	*SD*	Range
Age (years)	73.62	6.58	60–84	73.94	6.28	63–84
Education (years)	14.38	3.07	8–19	13.08	3.09	9–20
Mattis Dementia Rating Scale	80.38	29.83	17–122	77.95	30.20	20–124
Mini-Mental State Exam	13.00	6.45	0–21	11.7	7.77	0–23
Physical Self-Maintenance Scale*	7.18	1.67	6–12	7.41	1.66	6–13

*$n = 17$ for both groups due to missing data.

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Table 2. FLOPs items with significantly different endorsement rates for AD patients with and without psychotic symptoms

Item	FLOPs	*p*-value
2. Is easily angered or irritated, has emotional outbursts without good reason.	Disinhibition	.008
10. Does or says embarrassing things.	Disinhibition	.003
12. Can't sit still, is hyperactive.	Disinhibition	.006
23. Starts things but fail to finish them, "peter out."	Apathy	.003
39. Cares about his/her appearance (for example, daily grooming)*.	Apathy	.009
42. Does things without being requested to do so*.	Apathy	.003

Note. Psychotic AD patients ($n = 20$) were rated significantly higher ($p < .01$; Mann–Whitney *U* test) by caregivers than never-psychotic AD patients ($n = 21$) for all six items. FLOPs = Frontal Lobe Personality Scale.
*Response scale is reversed for these items.

DISCUSSION

AD patients with psychotic symptoms exhibited a significantly greater degree of neurobehaviors associated with frontal dysfunction than AD patients without psychotic symptoms matched for dementia severity. These findings are consistent with neuropsychological and clinicoanatomical evidence indicating an association between executive and frontal dysfunction and psychotic symptoms in AD. The neurobehavioral syndromes exhibited by AD patients with psychotic symptoms are those typically considered more characteristic of subcortical dementia (e.g., dementia due to Huntington's disease) rather than cortical dementias such as AD (Cummings, 1993). Thus, our findings in concert with past research suggest that AD with psychotic symptoms is anatomically, neuropsychologically, and behaviorally distinct from AD without psychotic symptoms and lend further empirical support to the subtyping of AD based on the presence of delusions (APA, 1994).

Our findings are consistent with extensive data linking behaviors associated with increased frontal dysfunction to psychotic symptoms in AD (e.g., Cummings & Kaufer, 1996; Förstl et al., 1991; Sultzer, 1996; Zubenko et al., 1991) and provide preliminary evidence indicating which specific behaviors are associated with psychotic symptoms. The differences between patients with and without psychotic symptoms were largely characterized by disinhibition and irritability and, to a lesser degree, by apathy and akinesia. Thus, based on preliminary evidence from this investigation, AD patients with psychotic symptoms might be expected to exhibit more impulsive and irritable behaviors and fewer behaviors reflecting motivation, self-control, and engagement than AD patients without psychotic symptoms matched for level of cognitive impairment. AD patients with and without psychotic symptoms could be expected to exhibit high levels of executive dysfunction given that mean scores were elevated on this scale for both groups.

Our findings are also consistent with past research that has established links between psychotic symptoms and behavioral problems in AD (Flynn et al., 1991; Kotrla et al., 1995; Lopez et al., 1991; Morriss et al., 1990). A somewhat unexpected finding was that participants diagnosed with psychotic symptoms were not significantly more impaired on a functional measure of self-care than patients without these symptoms, suggesting that the behavioral differences associated with psychotic symptoms are not merely a reflection of functional disability. However, this finding is in contrast to those reported by previous investigators (e.g., Stern et al., 1994) and this inconsistency suggests that this is an issue in need of further study. Additionally, the failure to detect a significant difference between patient groups in our sample may have been due to floor effects on our measure. Distributions of scores for AD patients with and without psychotic symptoms were both skewed with an overrepresentation of scores at the lowest end of the scale. It is possible that a more sensitive functional measure may have detected differences that were not apparent on the brief six-item measure used in the study.

Investigation of behavioral dysfunction in AD is important because of associations with caregiver distress (Bedard et al., 1997; Kaufer et al., 1998; Rabins et al., 1982) and premature institutionalization (Chenier, 1997; Chenowith & Spencer, 1986; Lieberman & Kramer, 1991; Steele et al., 1990). Although previous investigations have already established links between psychotic symptoms and behavior problems in AD, this is the first investigation to examine associations between psychotic symptoms and specific neurobehavioral syndromes associated with frontal dysfunction. However, increasing evidence indicates that assessment of these behaviors in AD is critical. For example, neurobehavioral dysfunction associated with frontal regions in AD has been linked to an advanced rate of disease progression (Mann et al., 1992) and to increased need for care and supervision (Royall et al., 1993). Thus, our findings highlight the importance of a comprehensive assessment of all aspects of AD, cognitive, functional, and behavioral, in order to fully characterize the presentation of the disease.

Several limitations of the current study need to be recognized. First, the generalizability of findings is limited by the fact that participants in the current sample were severely demented. Thus, future research is needed to determine if our findings apply to mild or moderately demented AD patients diagnosed with psychotic symptoms. A second limitation of the study is that hallucinations and delusions

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were not analyzed separately. Preliminary evidence suggests that these two types of psychotic symptoms may have different correlates (Ballard et al., 1995). For example, Burns et al. (1990a, 1990b) found a positive association between hallucinations and greater cognitive deterioration over time but discovered no correlation between delusions and cognitive deterioration. Finally, the small sample sizes in this study resulted in decreased statistical power and increased likelihood of false negative errors. However, the fact that predicted findings emerged despite compromised statistical power is encouraging. Additional data are being collected in a prospective design to further investigate the major hypothesis of this study that predicts a unique positive association between neurobehaviors associated with frontal dysfunction and psychotic symptoms in AD.

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