



Predicting Behavioral Dysfunction in Alzheimer's Disease

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Abstract

Many patients with Alzheimer's disease (AD) experience significant behavioral dysfunction that ultimately results in placement in managed care facilities. Right frontal lobe dysfunction is associated with a range of behavioral problems. Most patients with AD experience greater degeneration of the left hemisphere. However, some patients experience relative right hemisphere dysfunction and the possibility exists that these patients are more likely to exhibit significant behavioral deficits. The purpose of this study was to examine whether neuropsychological tests of right and left frontal lobe functioning may predict behavioral dysfunction in patients with AD. A total of 20 patients with AD were administered neuropsychological tests of left and right frontal lobe functioning and given the Neuropsychiatric Inventory Questionnaire as a measure of behavioral dysfunction. The result of a multiple regression indicated that the measure of right frontal lobe functioning was the best predictor of behavioral dysfunction. These findings have important implications in predicting patients who might experience significant behavioral dysfunction and hence greater likelihood of placement in a managed care facility.

Key words: Alzheimer's Disease; Behavioral Dysfunction; Prediction; Frontal Lobes

Introduction

Many patients with Alzheimer's disease (AD) will eventually be placed in managed care and these admissions are often the result of significant behavioral problems as opposed to the memory disturbances that accompany the disease [1] reported an increased likelihood of disruptive behaviors in older adults who were at high risk of being institutionalized [2] conducted a one-year longitudinal study to investigate behavioral and psychological symptoms in patients with AD who were institutionalized versus those who were not institutionalized. Patients who were institutionalized exhibited higher agitation and disinhibition scores from the Neuropsychiatric Inventory, as well as lower Mini Mental Status Examination scores

and increased caregiver burden. Agitation and aggression have been correlated with caregiver burden [3] and studies have found caregiver emotional distress and burden is significantly related to nursing home admission [4-6]. Hence, the expression of agitation, aggression, and disinhibition appear to be key factors in whether patients with dementia are eventually admitted to nursing homes or other managed care facilities.

Agitation, aggression, and other problematic social behaviors have been consistently related to right frontal lobe dysfunction and reduced capacity for regulatory control. Capacity limitations in these right frontal regions may leave negative emotional analyzers

unregulated and even unbridled under duress or more extreme stress [7-10] proposed a neuropsychological model of hostility that related hostility and violence-prone behavior to problems with self-awareness from right cerebral dysfunction, with specific implications for the right frontal lobe [11] reported the case of an individual who exhibited aggression and callous disregard for others following trauma to the right frontal region. Ictal episodes of aggression related to a right frontoparietal epileptiform focus have also been reported [12]. Relatively increased left frontal and decreased right frontal activity has been associated with anger and aggression [13,14]. Research has also indicated that agitation in patients with AD is associated with reduced cerebral blood flow in the right inferior frontal gyrus [15]. Finally, [16] found right frontotemporal involvement in frontotemporal dementia patients with acquired sociopathy.

Many studies have related disinhibition to right frontal lobe functioning, particularly the right inferior frontal cortex [17]. Behavioral disinhibition tasks administered to healthy individuals activate the right middle frontal gyrus and right dorsolateral prefrontal cortex [18]. Injuries and lesions to the right orbitofrontal and basal temporal area have been associated with inappropriate social behaviors and other disinhibition behaviors [19]. Patients with degenerative diseases may exhibit this relationship between right frontal functioning and disinhibition. For instance, patients with frontotemporal dementia exhibit socially inappropriate behaviors and problems with disinhibition [20]. Others have reported a relationship between disinhibition and activation within regions of the right frontal lobe [21-23].

The neuropathological processes of AD follow a typical pattern, with initial involvement of the entorhinal cortex followed by the hippocampus, then other regions of the temporal lobe and association cortex, and finally involvement of the frontal lobes or orbitofrontal region [24-26]. However, there are lateral cerebral asymmetries to these neuropathological processes. Specifically, whereas both hemispheres are associated with a loss of gray matter, increased gray matter loss in the left hemisphere has been recorded in many patients with AD [27-29]. Asymmetry in cerebral glucose metabolism has also been reported [30].

The asymmetries in gray matter loss and cerebral glucose metabolism may be associated with different patterns of memory, cognitive, and behavioral deficits. For instance, greater left hemisphere atrophy has been associated with lower verbal abilities in patients with AD [31,32] reported four cases of patients with AD, three of whom had relative left hemisphere atrophy and presented with language deficits initially and one patient with relative right hemisphere atrophy who presented with predominant visuospatial problems as the first complaint. Other researchers have found relatively diminished metabolism in the left hemisphere for AD patients with predominant language dysfunction and relatively diminished metabolism in the right hemisphere for patients with predominant visuoconstructive dysfunction [33,34] conducted a factor analysis based on neuropsychological test performance and found two factors, including a verbal and a visuospatial factor. Their

results also indicated that over one quarter of the patients exhibited asymmetry on their profile of deficits from neuropsychological testing. Further, these asymmetries persist and remain stable throughout the disease process [35].

Given the right frontal lobe involvement in aggression, disinhibition, and socially disruptive behaviors the possibility exists that patients with AD who have relatively greater right hemisphere involvement are at increased risk for developing significant behavioral problems. These emotional deficits, with increased sympathetic drive, poor insight to deficits, and negative emotional displays may be found in patients with right hemi-aging [29]. Hence, based on neuropsychological testing, it may be possible to predict patients who will later exhibit the aggression and disinhibition that ultimately results in placement in managed care facilities. Predicting patients who may develop significant problems with aggression and disinhibition would enable the families of these patient's time to plan for appropriate treatments and interventions and also possibly begin addressing these problems earlier in the course of the disease. However, whereas many studies have examined the behavioral variables that predict nursing home placement, there has been a veritable paucity of research examining the prediction of the behavioral problems that lead to placement. An investigation by Galynker et al. (2000) [36] is among the few and they found that decreased perfusion in the frontal cortex was associated with negative symptom severity, but not with measures of cognitive functioning. However, neuropsychological assessment in this project was restricted to the use of the Mini Mental Status Examination (MMSE) as the measure of cognitive functioning. The purpose of the present study was to determine if neuropsychological test performance could predict scores on a measure of behavioral dysfunction in patients with AD. Given the aforementioned role of the right frontal lobe in aggression and disinhibition, we predicted that a measure of right frontal lobe functioning would constitute the best predictor. Research has found that the Ruff Figural Fluency Test (RFFT) is sensitive to right frontal lobe functioning [37]. Additionally, we have previously reported that heightened delta EEG amplitude over the right frontal lobe is predictive of reduced performance on the RFFT [38]. Performance on the Controlled Oral Word Association Test (COWAT), in contrast, is associated with left frontal lobe functioning [39-43]. Our specific prediction was that the RFFT would be the better predictor of behavioral dysfunction as measured by the Neuropsychiatric Inventory (NPI), followed by a measure of general cognitive functioning (MMSE), whereas performance on the COWAT was expected to make a nonsignificant contribution to the model.

Methods

Participants

The sample consisted of 20 patients diagnosed with probable AD (8 men and 12 women) with an age range of 66 to 87 years ($M = 73.70$, $SD = 6.67$) and an average education level of 11.45 years ($SD = 3.09$). The diagnosis of probable AD met NINDS-ADRDA and DSM-V criteria. Scores on the Mini Mental Status Exam ranged from 18 to 28 ($M = 23.40$, $SD = 3.00$). The patient sample was drawn

from patients who were referred to the Memory Disorder Clinic at the Murfreesboro Medical Clinic to complete a neuropsychological evaluation for memory problems.

Apparatus

Mini Mental Status Exam: The Mini Mental State Exam (MMSE) is a screening test used to assess general cognitive functioning. Areas of functioning assessed include orientation, registration, attention, recall, working memory, language, and construction or drawing ability. The range of scores possible is from 0 to 30 and the raw score was used for this study.

Neuropsychiatric Inventory Questionnaire: The Neuropsychiatric Inventory Questionnaire [44] is a brief form of the Neuropsychiatric Inventory [45] consisting of 12 questions assessing behavioral changes and dysfunction in patients with neurological illnesses. Behaviors are rated in terms of severity on a scale of 1 to 3 and in terms of the degree of caregiver distress on a scale of 0 to 5. The specific behaviors rated include delusions, hallucinations, agitation or aggression, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbances, nighttime behaviors, and appetite and eating behaviors. The total severity rating across all behaviors included was used for the purpose of this study.

Controlled Oral Word Association Test: The Controlled Oral Word Association Test (COWAT) requires the subject to name as many words as possible that begin with a specified letter (F, A, and S) within 60 seconds. However, they cannot use proper nouns, they cannot count, and they cannot use a stem word and then simply provide different endings. The variable of interest for this study was the total number of words produced across the three different letters used in the test.

Ruff Figural Fluency Test: The Ruff Figural Fluency Test [46] is a measure of nonverbal fluency consisting of five individual parts, with each part consisting of a unique stimulus pattern. More specifically, each of the five parts contains a 5 x 7 array of 35 unique stimulus items, with each stimulus item being comprised of a 5-dot matrix. The test involves drawing as many unique designs as possible by connecting two or more of the dots within each of the matrices within a time limit of one-minute. The first three trials contain the same stimulus pattern but with different distracters placed in the background. The fourth and fifth trials each contain

a different 5-dot matrix. The total number of unique designs produced across the five trials was used in this study.

Procedure

This study was approved by the Middle Tennessee State University Institutional Review Board and all participants were treated in accordance with the ethical principles of the American Psychological Association. Participants were evaluated at Murfreesboro Medical Clinic, a large clinic located in middle Tennessee. The COWAT, MMSE, NPI-Q, and RFFT were administered as part of a larger neuropsychological test battery, the purpose of which was to assess for and diagnose dementia. Each test was administered according to the standardized procedures or administration protocols.

Results

The data were initially analyzed by examining the correlations between the NPI-Q and the RFFT, MMSE, and COWAT. A Bonferroni correction was used to control for conducting multiple correlations ($p < .017$). The results indicated a significant correlation between the NPI-Q and the RFFT ($r = -.64$, $p = .002$, $r^2 = .41$) and also between the NPI-Q and the MMSE ($r = -.52$, $p = .013$, $r^2 = .27$). The correlation between the NPI-Q and the COWAT was not significant ($r = -.42$, $p = .04$). The variables were then entered into a multiple regression, using the Enter method. The NPI-Q was the dependent variable and the predictors included the RFFT, MMSE, and COWAT, entered in that order. The RFFT was entered first, given that it is a measure of right frontal lobe functioning. Therefore, it should have the strongest relationship with behavioral dysfunction (NPI-Q) and be the best predictor of NPI-Q outcome scores. The MMSE was entered second, since it is a measure of general cognitive functioning. Finally, the COWAT was entered last since it is a measure of left frontal lobe functioning and should therefore be the weakest predictor of NPI-Q outcome scores.

The result indicated that the RFFT was a significant predictor of the NPI-Q scores. Moreover, the addition of the MMSE and the COWAT did not significantly improve the basis for predicting the NPI-Q scores (see Table 1). Finally, we sought to determine if the aforementioned correlations between the variables of interest were significantly different [47]. The results indicated that no significant differences existed between any of the correlations (see Table 2).

Table 1: Hierarchical linear regression results.

Model	B	Std. Error	Beta	t	p	R	Adj. R ²	Change Statistics		
								R ²	F	p
1 (Constant)	15.83	2.93		5.41	<.001	.64	.38	.41	11.2	.004
RFFT	-0.22	0.07	-0.64	-3.35	0.004					
2 (Constant)	22.5	8.12		2.77	0.014	.66	.37	.03	0.78	.392
RFFT	-0.18	0.08	-0.51	-2.13	0.051					
MMSE	-0.36	0.41	-0.21	-0.88	0.392					

3 (Constant)	22.33	9.95		2.25	0.041	.66	.32	.00	0.001	.975
RFFT	-0.18	0.09	-0.51	-2.03	0.062					
MMSE	-0.35	0.54	-0.21	-0.65	0.529					
COWAT	-0.004	0.12	-0.01	-0.03	0.975					

Table 2: Test results for differences between correlations.

Correlations Compared	Z	p
NPI-Q with RFFT (-.64)	-0.68	0.248
NPI-Q with MMSE (-.52)		
NPI-Q with RFFT (-.64)	-1.09	0.138
NPI-Q with COWAT (-.42)		
NPI-Q with MMSE (-.52)	-0.61	0.271
NPI-Q with COWAT (-.42)		

Discussion

The results of this study supported the hypothesis investigated. Specifically, a significant negative correlation was found between the NPI-Q and the RFFT, indicating that as scores on the NPI-Q increase scores on the RFFT decrease. Hence, increasing behavioral dysfunction as measured by the NPI-Q is associated with increasing right frontal lobe dysfunction as measured by the RFFT. Further, the results indicated that performance on the RFFT is a significant predictor of NPI-Q scores and that the MMSE and COWAT measures did not improve the prediction of NPI-Q scores. Hence, as predicted, right frontal lobe dysfunction was associated with and predicted behavioral dysfunction in patients with Alzheimer's disease. There have been a few reported studies examining the relationship between cognitive functioning and behavioral dysfunction in patients with Alzheimer's disease. However, the findings of these studies have been somewhat mixed. Some researchers have failed to find a significant relationship between cognitive functioning or decline and behavioral disturbances [48, 49] or psychosis [50]. However, Cooper and colleagues reported that a number of behavioral variables were related to declining cognitive functioning [51]. Further, an association between cognitive decline and physical aggression in patients with AD has been reported [52]. The equivocal findings regarding the relationship between cognitive functioning and behavioral disturbance may be a result of the fact that these studies have all only used indices of general cognitive functioning, such as the MMSE. The present study is the first to use more specific neuropsychological measures to examine this relationship and the first to support that behavioral dysfunction may be specifically related to right frontal lobe dysfunction in patients with AD.

As mentioned previously, many patients with AD will be placed in managed care facilities. The presence of significant behavioral dysfunction leads to increased caregiver distress and increases the likelihood that patients with AD will be admitted to a nursing home. The ability to predict patients who may experience behavioral dysfunction would enable the family and caregivers valuable time for planning and provide important educational information regarding the potential for behavioral dysfunction and the types

of behaviors that may be experienced. Further, treatments may be initiated earlier for those patients who are identified as being at increased risk. As a result, admission to managed care facilities may be delayed, which would have a significant monetary benefit for the patients and their families.

Although the present study found that performance on a measure of right frontal lobe functioning predicted behavioral dysfunction in patients with AD, the study was retrospective in nature. A more prospective, longitudinal study using the same neuropsychological tests would help to substantiate the present findings. Future research may also benefit from including additional measures of right versus left frontal lobe functioning to determine if the prediction of behavioral dysfunction may be increased. Finally, the present study inferred right frontal lobe functioning based on performance on a test that is purported to be sensitive to this region. Additional research may seek to include anatomical measures to corroborate the presence of relative right frontal dysfunction, such as by assessing gray matter loss or using functional imaging.

Acknowledgment

None.

Conflict of Interest

No conflict of interest.

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