Predictors of Depressive Symptoms in Persons With Alzheimer’s Disease

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In a 4-year longitudinal study, we evaluated factors related to the development of depressive symptoms in 410 persons with Alzheimer’s disease. We measured depressive symptoms annually by using the 17-item Hamilton Rating Scale, which we completed by using structured interviews with family members. On the basis of informant ratings of premorbid personality, we associated neuroticism with a higher rate of depressive symptoms, particularly mood disturbances. We associated greater cognitive impairment with a small reduction in mood symptoms and a modest increase in somatic symptoms. Among demographic variables, somatic symptoms were more common in men and mood symptoms were inversely related to age. Depressive symptoms in Alzheimer’s disease appear to follow a more predictable pattern of expression than previously described.

A complex relationship exists between Alzheimer’s disease (AD), a late-life neurodegenerative disorder, and depression. An increase in depressive symptoms often precedes the onset of detectable cognitive impairment in persons who develop AD (Berger, Fratiglioni, Forsell, Winblad, & Backman, 1999), and it may indicate an increased risk of the disease (Devanand et al., 1996; Wilson et al., 2002). Depressive symptoms also frequently occur during the course of AD. In cross-sectional surveys, clinically significant levels of depressive symptoms are generally found in 15–30% of persons with AD (Teri & Wagner, 1992), although few meet diagnostic criteria for major depression (Weiner, Edland, & Lusczynska, 1994). Depressive symptoms appear to occur sporadically, often as relatively brief episodes (Brodaty & Luscombe, 1996). However, less is known about factors that may predispose persons to develop depressive symptoms in AD.

In the present study, we explore two factors that may contribute to the development of depressive symptoms in AD. One is the individual’s lifelong pattern of emotional responses or temperament as indexed by premorbid personality. This emotional phenotype presumably reflects the cumulative effects of genetically determined neural patterns and experience. The second is disease severity, which reflects the cumulative impact of changes in brain structure and chemistry, as indexed by level of cognitive impairment.

Premorbid Personality

In the general population, depressive symptoms and syndromes have been closely linked to specific personality characteristics. In particular, the dimension of “neuroticism” is associated with an increased risk of the clinical syndrome of depression (Enns & Cox, 1997) and with an increased frequency of negative emotional states (Watson & Tellegen, 1985). Persons with high levels of neuroticism are viewed as more likely to experience intense negative emotion when faced with aversive events (Eysenck, 1967). Thus, neuroticism can be seen as a critical component of adaptive potential, providing information about the amplitude of an individual’s response to stress. Neuroticism appears to be relatively stable over the life span (Costa & McCrae, 1988), but the utility of this attribute in understanding affective disturbances in persons with AD remains uncertain.

One possibility is that a lifelong predisposition toward negative emotion, reflected as the level of premorbid neuroticism, may be associated with increased vulnerability to affective disturbances after the onset of AD. Previous tests of this hypothesis have found a trend for increased depressive symptoms in relation to premorbid neuroticism (Chatterjee, Strauss, Smyth, & Whitehouse, 1992; Low, Brodaty, & Draper, 2002; Meins, Frey, & Thiesemann, 1998; Migliorelli et al., 1996; Strauss, Lee, & DiFilippo, 1997; Swearer, Hoople, Kane, & Drachman, 1996), but this effect has been consistently small and rarely statistically significant. Other findings point to substantial changes in personality during the course of AD (e.g., Aitken, Simpson, & Burns, 1999; Petry, Cummings, Hill, & Shapira, 1994), including increasing levels of neuroticism. One interpretation of these findings is that there is limited continuity between patterns of emotional reactivity before and after disease onset.

To date, the association between premorbid personality and depressive symptoms in AD has been evaluated in small, cross-sectional studies with several important methodological limitations. Statistical power is likely to be limited by the inclusion of fewer than 100 participants in most previous studies, particularly in light of the modest rate of depression in persons with AD. Second, there is no separation in time between informant ratings of premorbid personality and current depressive symptoms, which increases the potential for measurement bias. Finally, because of the apparent episodic nature of depression in persons with AD, a single assessment may not adequately reflect disease-related affective disturbances.

Level of Cognitive Impairment

There is evidence that emotional regulation improves with age (e.g., Gross et al., 1997; Lawton, Kleban, Rajagopal, & Dean, 1992), but these regulatory mechanisms may be compromised by the neurodegenerative processes associated with AD. Level of cognitive impairment is the most widely
adopted marker of disease-related functional capacity. There is evidence that the ability to comprehend emotion conveyed in facial expressions and voice prosody declines in relation to increased severity of cognitive impairment in persons with AD (Albert, Cohen, & Koff, 1992), which may impair emotional regulation in social interactions. However, the ability to express emotion appears to be preserved well into the advanced stages of the disease (Lawton, Van Haitsma, & Klapper, 1996; Magai, Cohen, Culver, Gomberg, & Malatesta, 1996). Thus, as the disease progresses, there may be a mismatch between capacities for emotional regulation and expression, perhaps setting the stage for affective disturbances.

No clear pattern of relationship between depressive symptoms and severity of cognitive impairment in persons with AD has emerged from previous studies. Findings range from reports of no association (Migliorelli et al., 1995; Reifler, Larson, Teri, & Poulsen, 1986), to positive correlation (Rovner, Broadhead, Spencer, Carson, & Folstein, 1989; Troisi et al., 1993), to negative correlation (Brodaty & Luscombe, 1996; Burns, Jacoby, & Levy, 1990; Fischer, Simanyi, & Danielczyk, 1990) between depression and level of cognitive impairment. However, most studies have relied on the clinical diagnosis of major depression as the index of affective disturbance. This approach has two potential limitations. First, effective criteria for the diagnosis of depression in persons with dementia have not been established (Olin, Katz, Meyers, Schneider, & Lebowitz, 2002), possibly undermining reliable classification. Second, depressive disturbances are likely to occur as a continuum in terms of the type and severity of symptoms, which will not be fully captured by syndrome definition. It is possible that quantitative measures of depression may improve sensitivity to associations with cognitive impairment, particularly with repeated measurement over a long period of time.

**Study Objectives**

In the present study, a large AD cohort was recruited from a dementia clinic and received annual evaluations over a 4-year period, with over 90% participation in follow-up among community-dwelling survivors. Our primary objectives were to (a) describe the temporal patterns and rates of depressive symptoms during the course of AD; (b) evaluate the relationship between premorbid personality ratings and depressive symptoms; and (c) evaluate the use of level of cognitive impairment as an index of disease severity. We evaluated personality ratings at study baseline as a predictor of depressive symptoms reported during four follow-up examinations. This design provides temporal separation between personality and depression, along with multiple assessments of depressive symptoms over time for enhanced stability in classification, addressing the key limitations of previous cross-sectional methods. We also broke down depressive symptoms into mood and somatic symptoms to examine whether these components are differentially associated with personality ratings or severity of cognitive impairment.

There were two primary hypotheses. First, will there be an increase in depressive symptoms in persons with higher levels of the personality dimension of neuroticism? No specific prediction was made for the dimension of extraversion because the relationship between extraversion and depressive symptoms is modest in the general population. Second, will depressive symptoms decline in frequency in conjunction with severity of cognitive impairment? Based on the suspected cognitive contributions to mood (Frijda, 1993), depressive symptoms should decrease with increasing cognitive impairment.

As secondary hypotheses, we examined differences in pattern between mood and somatic symptoms of depression. Neuroticism is associated with increased expressed negative emotion and increased somatic complaints in the general population (Costa & McCrae, 1985; Watson & Tellegen, 1985). As an extrapolation, we tested the hypothesis that neuroticism is associated with increased mood and somatic symptoms of depression. We examined other factors in relation to depressive symptoms, including age, gender, and the presence of other chronic medical conditions, with hypotheses related specifically to mood and somatic symptoms. Mirroring gender differences in depressive disorders (Bebbington et al., 1998), men were expected to exhibit fewer mood symptoms. Because health-related limitations increase with age, particularly for older men, somatic depressive symptoms were expected to be significantly associated with age and gender. Finally, other chronic medical conditions were expected to increase the likelihood of somatic symptoms.

**Methods**

**Participants**

The sample consisted of 410 persons recruited through the Rush Alzheimer’s Disease Center (RADC). At study entry, we required participants to (a) meet accepted diagnostic criteria for AD (McKhann et al., 1984), (b) initially dwell in a noninstitutional setting, and (c) have a Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score above 10; we excluded persons with severe dementia at baseline to limit floor effects in measuring change in cognitive and physical function. Evaluations at the RADC followed a standardized protocol (Morris et al., 1989), including medical history, neurological evaluation, neuropsychological testing, and laboratory tests. To rule out structural lesions of the brain, we obtained MRI scans for individuals without a CT or MRI study performed within the past 12 months or if clinically indicated by recent events. The diagnosis of AD required a history of cognitive decline and evidence of impairment in memory and at least one other cognitive domain, but it included people with coexisting medical conditions. A neurologist assigned diagnoses after review of all materials.

Over a 12-month period, 491 persons met eligibility requirements and 410 (83%) were recruited into the study. Procedures approved by the Institutional Review Board at Rush University Medical Center were followed, in that signed consent was obtained from participants and a family member.

**Measures and Procedures**

In this prospective study, participants were evaluated at baseline and at up to four annual follow-up examinations. To maintain the independence of observations over time, examiners were blind to previously collected information. This study relied exclusively on informant ratings of personality and depressive symptoms. The validity of self-report is closely related to level of cognitive impairment, a primary study hypothesis. By contrast, informant ratings can be uniformly
obtained across repeated measurements (time) and across levels of cognitive impairment.

**Premorbid personality.** — At study baseline, we measured two dimensions of premorbid personality most closely identified with emotional reactivity, that is, neuroticism and extraversion, by using scales developed and validated by Goldberg (1992). In a pilot study with 30 participants, informant ratings were compared on two measures of personality based on the Big Five factor scheme: NEO-FF (Costa & McCrae 1992) and the Adjective Rating scale of Goldberg (1992). Due to time required to complete and missing items were substantially greater for the NEO-FF, the Goldberg scales were adopted in this study. Correlations between the NEO-FF and Goldberg scales on the dimensions of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness were adequate (r = .59–.84). In the study cohort, score distributions for agreeableness and conscientiousness were psychometrically inadequate, clustering near the maximum score of 20 (agreeableness, M = 17.5; conscientiousness, M = 17.1). Although regression coefficients were not significant for these three scales in preliminary analyses on any measure of depressive symptoms, null findings for agreeableness and conscientiousness should not be regarded as meaningfully interpretable. For this reason, we present only data from two dimensions of emotional reactivity, neuroticism and extraversion, to test study hypotheses.

The 20-item scales developed and validated by Goldberg consist of descriptive adjectives, which are rated in a true–false format. Scores are based on the total number of items endorsed. We modified original scale instructions to include the following statements: "To fully understand the changes that take place with Alzheimer's disease, it is important to understand what a person is like before the disease started. Rate each item based on how you would describe your family member about 5 years before he or she started to have memory problems." This measure was selected because of its minimal task complexity and time burden for family members of the participant. In 369 persons with AD, internal consistency estimates for each scale were adequate (neuroticism, r = .69; extraversion, r = .84). The low correlation between neuroticism and extraversion (r = −.18, p < .05) suggests that these dimensions are relatively independent.

**Cognitive impairment.** — We selected the MMSE (Folstein et al., 1975) as the primary index of cognitive impairment because of its widespread use in scaling dementia severity. Scores range from 0 to 30, based on the number of correct responses; thus, lower scores indicate greater severity of cognitive impairment. To account for changes in cognitive impairment over the course of the study, we assessed the MMSE concurrently with depression and included it in all analyses as a time-varying predictor.

**Other covariates.** — Demographic variables included age (in years), gender (0 = female, 1 = male), and race (0 = Caucasian, 1 = African American). The number of other common chronic medical conditions was scored as the sum of informant-reported physician-diagnosed conditions: hypertension, diabetes, cancer, and coronary artery disease.

**Depressive symptoms.** — We assessed depressive symptoms by using the 17-item Hamilton Rating Scale for Depression (HRS-D; Hamilton, 1960), with scores ranging from 0 to 56. Specific implementation of the HRS-D was based on the structured interview format modified for use with an informant (Gilley et al., 1995). To enhance the uniformity of caregiver ratings, we based the presence and severity of depressive symptoms on observations during the month preceding each clinical evaluation. HRS-D scores do not appear to be systematically related to informant characteristics (Gilley & Wilson, 1991), including the relationship between participant and informant.

To examine types of depressive symptoms, we broke down HRS-D total scores into mood (5 items) and somatic symptom (12 items) subscales on the basis of the partition of items adopted in previous studies (Lazarus, Newton, Kohler, Lesser, & Schweon, 1987; Troisi et al., 1993). We evaluated this proposed scheme by using a factor analysis of baseline HRS-D scores (which are not used to test study hypotheses). A principle components analysis revealed seven factors with eigenvalues in excess of 1, which account for 65.9% of the variance. The mood subscale was represented by two factors; the remaining five factors consisted of clusters of somatic symptoms. Internal consistency was .73 for the mood symptoms subscale and .42 for the somatic symptoms subscale. These data support the partition of the HRS-D into mood and somatic symptoms, but they suggest some limitations in homogeneity. There was a modest correlation between mood and somatic symptom scores at baseline (r = .26, p < .01).

Interviews to complete the HRS-D were conducted by formally trained research assistants, blind to other clinical data. Training procedures included didactic sessions, audiotapes, and supervised administration. Interrater reliability was evaluated annually during the study. A total of 30 participants were randomly selected at each measurement point to evaluate interrater reliability between the interviewer and study coordinator. These interviews were conducted jointly, with the study coordinator identified as an observer for training purposes. Interview data were scored independently. Estimates of interrater reliability ranged from .87 to .92 across the five study observations.

**Analytic Methods**

We collected variables used in these analyses at five time points during the study. We measured the following variables only at study baseline: demographic characteristics (age, gender, and race), other chronic medical conditions, and premorbid personality (neuroticism and extraversion). We measured level of cognitive impairment (MMSE) and depressive symptoms (HRS-D total, mood, and somatic symptoms) annually for up to four years (observation points 2–5). We fit regression models for the vector of four measurements of depressive symptoms over time according to the generalized estimating equation (GEE) approach (Liang & Zeger, 1986) as executed in SAS PROC GENMOD (SAS, 1996). These models are highly flexible, allowing a choice of relationship between the outcome and the predictor, relationship of the variance to the expected outcome, and within-person correlation. We selected a binomial error structure to reflect the greater error variability near the middle of the scale. Finally, we assumed a within-person correlation of errors to be identical for each pair of times of observation (exchangeable error structure). We
Table 1. Summary of HRS-D Scores and Depressive Disorders at Four Annual Follow-Up Evaluations

<table>
<thead>
<tr>
<th>Measure</th>
<th>Follow-Up Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>HRS-D scores: $M$ ($SD$)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.6 (5.9)</td>
</tr>
<tr>
<td>Mood</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>Somatic</td>
<td>6.3 (4.6)</td>
</tr>
<tr>
<td>Depressive disorders: $n$ (%)</td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Subthreshold depression</td>
<td>34 (9.4)</td>
</tr>
<tr>
<td>HRS-D total scores $\geq$ 15</td>
<td>51 (14.2)</td>
</tr>
</tbody>
</table>

Notes: For follow-up years, 1 is $n = 360$; 2 is $n = 313$; 3 is $n = 279$; and 4 is $n = 188$. HRS-D = Hamilton Rating Scale for Depression.

Validated all models by using both graphical techniques and tests of alternative structures.

Results

At baseline, the sample (136 men and 274 women) ranged in age from 45 to 95 ($M = 75.5$ years, $SD 7.3$). Participants were Caucasian ($n = 349, 85.1\%$) or African American ($n = 61$ persons, 14.9\%). Other chronic medical conditions were common; 164 participants (40.0\%) were reported to have one condition and 119 (29.0\%) were reported to have multiple conditions. Informant ratings of premorbid personality indicated a wide range of scores on the neuroticism and extraversion scales. Neuroticism had a mean score of 7.1 ($SD = 4.8$) with a 7-point interquartile range (25th percentile $= 3$; 75th percentile $= 10$). Extraversion had a mean score of 11.9 ($SD = 4.7$) with an 8-point interquartile range (25th percentile $= 8$; 75th percentile $= 16$). Premorbid personality ratings were completed by a spouse for 210 participants (51.2\%), an adult child for 176 (42.9\%), and other relative for 24 (5.9\%). There was no significant difference in ratings between spouses and other informants for neuroticism (spouse: $M = 6.7, SD = 4.9$; other: $M = 7.5, SD = 4.7$) and extraversion (spouse: $M = 12.1, SD = 4.3$; other: $M = 11.3, SD = 4.7$). Finally, mean MMSE scores declined from 18.7 ($SD = 4.3$) at baseline to 7.1 ($SD = 5.1$) at the last evaluation, indicating an increase in the severity of cognitive impairment over the study period.

Follow-up participation rates among community-dwelling survivors at each observation ranged from 90.9\% to 95.1\%. Thus, missing observations that were due to participant reluctance were low, enhancing internal validity. However, length of follow-up was truncated by nursing home or death in 224 participants.

Table 1 shows average HRS-D total, mood, and somatic symptom scores by four follow-up evaluations. Although the HRS-D scores will be used to evaluate study hypotheses, descriptive information on depressive disorders is also provided for each evaluation. Note that the number of participants that met diagnostic criteria for major depression (American Psychiatric Association, 1994) was low at each evaluation, but the number was substantially higher for two indicators of clinically significant depressive symptoms. Subthreshold depression reflects substantial overlap with the criteria for major depression (evidence of mood disturbance and some associated symptoms), but with either insufficient duration of symptoms or number of associated symptoms. Subthreshold depressive phenomena were found in 9.0\% to 13.9\% of participants at follow-up evaluations. On the basis of HRS-D total scores greater than or equal to 15 to define depressive disturbances, 108 participants had significant depressive features on at least one evaluation, including 43 with disturbances on multiple evaluations. Together, these data suggest that clinically significant depressive symptoms were evident in approximately 15\% of this AD cohort at any given point in time.

We examined temporal patterns in depressive symptoms in three ways. First, we evaluated a GEE model regressing total HRS-D scores on study time. The coefficient for study time ($\Delta 20$) was not significant ($p > .20$), arguing against any systematic increase in depressive symptoms over time. Second, we used a binomial GEE model regressing the presence of HRS-D scores $\geq 15$ on study time to examine the temporal pattern of clinically significant periods of depressive symptoms. High levels of depressive symptoms did not significantly vary with study time. The sequence of periods with HRS-D scores $\geq 15$ over the 4 years of data collection was random. Finally, we evaluated interactions with study time for the following variables: neuroticism, extraversion, MMSE, age, gender, race, and other chronic conditions. (A contrast comparing HRS-D scores from spouse versus child informants was not significant and therefore not included in the models used to test study hypotheses outlined in the paragraphs that follow.) There were no significant interactions with study time, suggesting no detectable temporal effects. Taken together, these observations suggest that depressive symptom levels change sporadically over time.

Table 2 summarizes regression models for HRS-D total, mood, and somatic symptoms scores. With respect to premorbid personality, neuroticism was associated with significantly higher rates of depressive symptoms across all three HRS-D measures. However, the effect size associated with neuroticism was larger for mood symptoms (3.39) than for somatic symptoms (2.27). In contrast, extraversion was inversely related to depressive symptoms, but this effect only approached significance for mood symptoms.

It is possible that the effects of neuroticism may be accounted for by a small number of persons with history of psychiatric disturbances. In this AD cohort, a total of 39 participants had a history of psychiatric disorders prior to the onset of AD. When tested in the absence of neuroticism and extraversion scores, past psychiatric disorders were significantly associated with HRS-D total score (coefficient $= 2.04, p < .05$), with trends for HRS-D mood (coefficient $= 1.51, p = .21$) and somatic symptoms (coefficient $= 1.74, p = .08$). However, when a term for neuroticism was entered into the model, there was no significant relationship between prior history of psychiatric disorders and HRS-D scores ($p > .20$).

Level of cognitive impairment was also associated with significantly higher rates of depressive symptoms, but it differed in direction for mood and somatic symptoms. Lower MMSE scores, reflecting greater cognitive impairment, were related to substantially higher HRS-D somatic symptom scores (effect size $= 4.45$). The small positive association between
MMSE scores and HRS-D mood subscale suggests that mood symptoms decline slightly as cognitive impairment increases (effect size = 2.18).

HRS-D scores also differed as a function of age, gender, and race. Age was inversely related to all three measures of depressive symptoms, but the effects were only significant for HRS-D total and mood scores. Gender differences were primarily limited to somatic symptoms, which were higher in men, but there was a nonsignificant trend toward a higher rate of mood symptoms in women. Racial differences approached significance, with a trend for African Americans to exhibit fewer mood symptoms and more somatic symptoms than their Caucasian counterparts.

No index of variance accounted for is currently available for GEE regression models. However, as an illustration of the relative magnitude of model effects, a 7-point increment on the neuroticism scale (the difference between the 25th and 75th percentiles in this cohort) is associated with a mean increase of 1.01 points in HRS-D total scores at each follow-up observation. The effects of neuroticism are similar for mood symptoms (mean increase of 0.43 points) and somatic symptoms (mean increase of 0.57 points). Likewise, a 10-point decrement in MMSE score (the expected change over a 3-year period) is associated with a mean increase of 0.81 points in HRS-D total scores, which reflects the combined effect of a mean decrease of .22 points in mood symptoms and a mean increase of 0.99 points in somatic symptoms. A 10-year increment in age is associated with a mean decrease of 0.61 points in HRS-D total score; male gender is associated with a mean increase of 1.05 points in HRS-D somatic symptoms.

In the preceding analyses, we omitted baseline measures of depressive symptoms to facilitate temporal separation from ratings of personality. However, these analyses included persons with high rates of depressive symptoms at baseline, which has the potential to bias informant ratings of personality in this subgroup. To address this limitation, we excluded 93 persons with clinically significant levels of depression at baseline (HRS-D total scores > 15). Table 3 summarizes models for HRS-D total, mood, and somatic symptom scores in 276 participants. The overall pattern of results in this subgroup was similar to that for the entire cohort across all depressive symptom measures. Note that coefficients for age, gender, neuroticism, and extraversion were reduced, but the effects for MMSE score were essentially unchanged. These data continue to support the primary hypothesis that premorbid neuroticism is associated with a higher rate of depressive symptoms during the course of AD. Likewise, age, gender, and level of cognitive impairment appear to be robust predictors of specific facets of depression. Finally, we found larger coefficients for neuroticism and extraversion when we included baseline depressive symptoms (measured concurrently with personality) in the analyses ($\beta_{\text{neuroticism}} = .189$, $\beta_{\text{extraversion}} = -.085$). Thus, the reported effects are likely to be conservative estimates for these variables.

**DISCUSSION**

This 4-year longitudinal study examined predictors of depressive symptoms in 410 persons with AD. The focus was on premorbid personality as a marker of lifelong patterns of emotional expression and on level of cognitive impairment as a marker of disease severity. The vector of depressive symptoms at four time points did not reveal any systematic patterns of HRS-D scores over time. The premorbid personality dimension of neuroticism, cognitive impairment level, age, and gender were found to reliably predict higher rates of depressive symptoms. These findings suggest that depressive symptoms may follow a more predictable pattern of expression than previously described.

### Premorbid Personality

One major objective of the present study was to evaluate premorbid personality as a factor contributing to the development of depressive symptoms during the course of AD. The focus was on neuroticism and extraversion, the two major dimensions of personality tied most closely to emotional expression (Watson & Tellegen, 1985). Neuroticism, which reflects susceptibility to negative emotion, was associated with an increased rate of depressive symptoms in this study. Although neuroticism was most closely associated with mood symptoms on the HRS-D scale, there was also a marginally significant increase in somatic symptoms. In contrast, extraversion, which reflects susceptibility to positive emotion, was inversely associated with depressive symptoms. However, the effects associated with extraversion were small and only approached statistical significance for HRS-D mood symptoms.

Most previous studies have not found a reliable association between premorbid neuroticism and depressive disorders in persons with AD (Chatterjee et al., 1992; Low et al., 2002; Meins et al., 1998; Migliorelli et al., 1995; Strauss et al., 1997; Swearer et al., 1996). These findings cast some doubt on the interaction between patterns of emotional reactivity before and after the onset of AD. However, our observations are consistent with evidence linking personality and emotion in the general population. Neuroticism has been strongly associated with the
clinical syndrome of depression (Enns & Cox, 1997) and with episodes of negative emotion (Watson & Tellegen, 1985). There is also evidence that neuroticism is associated with more frequent somatic complaints (Costa & McCrae, 1985). The small inverse relationship between extraversion and depressive symptoms follows the pattern expected for this dimension (Enns & Cox, 1997). Unfortunately, without measures of positive emotion to serve as a counterpoint to depressive symptoms, our data provide an incomplete picture of the specificity of neuroticism and extraversion as predictors of emotional valence.

Several design characteristics of the present study strengthen the interpretation of the findings. The larger sample size and repeated assessment of depressive symptoms may have enhanced sensitivity to the effects of neuroticism. We also provided a more stringent test of the hypothesis by using a longitudinal design to ensure temporal separation between ratings of premorbid personality and depressive symptoms. Finally, we controlled for the effects of other variables, including level of cognitive impairment at each observation.

The interpretation of our data rests on the validity of the personality ratings as an index of premorbid status. Like previous studies in AD, the assessment of premorbid personality was based on retrospective ratings by a family caregiver. Unfortunately, no independent measure of premorbid personality was available to serve as a validity benchmark for these informant ratings. It is important to emphasize that validity coefficients for informant ratings of personality (relative to self-report) are modest (McCrae, 1982), with shared variance estimates rarely in excess of 25%. It seems reasonable to assume that measurement error is likely to be magnified when informants retrospectively rate personality characteristics.

The type of measurement error associated with the informant ratings of premorbid personality holds the key to interpretation. A random noise component, in which informant ratings of premorbid personality are inaccurate but independent of current patient characteristics, would result in an underestimate of the predictive value of premorbid personality. To the extent that informant ratings of premorbid personality are influenced by current status, the ratings reflect some mixture of lifelong and disease-specific attributes. This nonrandom error would result in an overestimate of the predictive value of premorbid personality characteristics. The longitudinal design of the present study, which provides temporal separation between ratings of premorbid personality and current depressive symptoms, offers some protection against this potential bias but cannot eliminate it. Thus, the contribution of premorbid personality to understanding disease-related emotional disturbances must be viewed with caution. In the most extreme case in which the informant ratings of premorbid neuroticism in this study provide no valid information about emotional reactivity prior to disease onset, our data suggest that ratings of neuroticism at one point in time have some predictive value with respect to subsequent depressive symptoms. If these ratings do convey some valid information about premorbid personality, then the results provide evidence of some continuity in a person’s predisposition toward negative emotion before and after disease onset.

**Cognitive Impairment**

This study provides evidence that depressive symptoms are reliably associated with level of cognitive impairment in AD. However, the pattern of association differed for mood and somatic symptoms. With increasing cognitive impairment over time, there was a small reduction in mood symptoms and a modest increase in somatic symptoms.

The direction and size of the relationship between cognitive impairment and depressive mood symptoms are noteworthy. If emotional regulatory mechanisms are successively impaired in persons with AD in conjunction with the severity of cognitive deficits, then the rate of negative emotion, including depressive mood symptoms, might be expected to increase over the course of the disease. The observed decline in mood symptoms is thus inconsistent with a generalized failure of emotional regulation.

There are several plausible explanations for a decline in mood symptoms with increasing severity of cognitive impairment in persons with AD. One possibility is that the experience of negative emotion is degraded as the severity of AD increases. As a result of limited cognitive capacity, situations that would typically evoke intense negative emotion may produce weaker or less persistent emotional responses. Unfortunately, there is little direct evidence regarding the subjective or physiological intensity of emotional reactions in persons with AD. Another possibility is that the ability to express emotion is degraded as the severity of AD increases. Studies of observed affect in persons with AD suggest that the capacity to express positive and negative emotion remains intact across a wide range of cognitive impairment (Lawton et al., 1996; Magai et al., 1997). However, some symptoms of depressed mood (e.g., guilt or poor self-esteem) may be more

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**Table 3. Regression Models Predicting HRS-D Total, Mood, and Somatic Symptom Scores Across Four Annual Follow-Up Evaluations, Excluding 93 Participants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HRS-D Total</th>
<th></th>
<th>HRS-D Mood</th>
<th></th>
<th>HRS-D Somatic Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
<td>p</td>
<td>Coefficient</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.061</td>
<td>0.029</td>
<td>.036</td>
<td>-0.028</td>
<td>0.011</td>
<td>.014</td>
</tr>
<tr>
<td>Gender: male</td>
<td>0.646</td>
<td>0.471</td>
<td>.188</td>
<td>-0.188</td>
<td>0.183</td>
<td>.305</td>
</tr>
<tr>
<td>Race: Black</td>
<td>0.646</td>
<td>0.585</td>
<td>.269</td>
<td>-0.212</td>
<td>0.227</td>
<td>.352</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>0.293</td>
<td>0.311</td>
<td>.349</td>
<td>0.010</td>
<td>0.091</td>
<td>.920</td>
</tr>
<tr>
<td>MMSE (0–30)</td>
<td>-0.081</td>
<td>0.026</td>
<td>.003</td>
<td>0.022</td>
<td>0.010</td>
<td>.028</td>
</tr>
<tr>
<td>Neuroticism (0–20)</td>
<td>0.129</td>
<td>0.053</td>
<td>.013</td>
<td>0.049</td>
<td>0.017</td>
<td>.004</td>
</tr>
<tr>
<td>Extraversion (0–20)</td>
<td>-0.043</td>
<td>0.051</td>
<td>.397</td>
<td>-0.029</td>
<td>0.019</td>
<td>.125</td>
</tr>
</tbody>
</table>

**Notes:** Excluded participants had significant depression at baseline (HRS-D total ≥ 15). HRS-D = Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination.
difficult to ascertain in persons with severe language impairment (Troisi et al., 1993).

The increase in somatic symptoms in conjunction with greater cognitive impairment, although statistically significant, was modest in size. Specifically, on average, there was only a 3-point increase in HRS-D somatic symptom subscale scores over the entire spectrum of cognitive impairment indexed by the MMSE. This finding is also compatible with evidence that specific somatic symptoms are more likely to occur in the later stages of AD, including sleep disturbances (Bliwise, 1993). An important element in the debate over diagnostic criteria for the syndrome of depression in persons with dementia is the weight assigned to somatic symptoms (Olin et al., 2002). Our data suggest that somatic symptoms may have limited predictive value for depression in persons with advanced dementia. Consideration should be given to differentially weighting the contribution of somatic symptoms based on level of cognitive impairment.

**Demographic Characteristics**

To date, there is no consistent evidence that age, gender, or race modify the risk of depressive symptoms in persons with AD. We found a small inverse relationship between age and symptoms of depressed mood in this AD cohort. This pattern is consistent with the relationship between age and negative emotion in the general population. Population-based studies of older adults have found an age-related decrease in depressive symptoms when other risk factors of depression are accounted for (e.g., Blazer, Burchett, Service, & George, 1991). There is also evidence of a reduction in the frequency and intensity of negative emotion with advancing age (Lawton et al., 1992; Levenson, Carstensen, Friesen, & Ekman, 1991). Further research is needed for us to understand whether age blunts depressive mood and other forms of negative emotion in persons with AD. This effect may also be an artifact of age cohort or other variables confounded with age.

Gender differences in depression tend to shrink with age, primarily as a result of a decline in rates for women after the age of 55 (Bebbington et al., 1998). Data from the present study suggest a complex relationship between gender and depressive symptoms in persons with AD. There was a nonsignificant trend toward a higher rate of mood symptoms in women, but the rate of somatic symptoms was significantly elevated in men. Several confounding factors, however, make the gender difference in somatic symptoms difficult to interpret. Adjusted for age and disease severity, the mortality rate for men in this cohort was double the rate for women. Thus, there may be important gender differences in health that are not captured by the variables included in this analysis. Likewise, at any given time during the study, less than 10% of men lived alone or with someone other than a spouse, compared with over 25% of women. As a result, ratings of somatic symptoms by caregiver informants may be less sensitive for women.

Finally, there was also a trend for racial differences in depressive symptoms in this study. Relative to Caucasian participants, African Americans tended to have a lower rate of mood symptoms and a higher rate of somatic symptoms. These differences, however, did not reach statistical significance. Because of the comparatively small number of African American participants included in this study, statistical power is limited with respect to racial differences. Replication of these findings in larger, more representative, samples of African American participants is needed.

**Methodological Considerations**

Inferences from the present study are enhanced by several design characteristics. Large sample size, long follow-up period, and high rate of follow-up participation increase power to detect associations with depression. The longitudinal design also permitted separation in time between ratings of premorbid personality and depressive symptoms. Concurrent measurement of cognitive impairment and depressive symptoms over a 4-year period may also provide a more reliable estimate of the relationship between these variables. Repeated measurements are particularly important because of the sporadic occurrence of depressive disturbances in persons with AD. Finally, depressive symptoms were broken down into mood and somatic composite scales, which were differentially associated with age, personality, and cognitive impairment.

Four major limitations should be considered in the interpretation of this study. First, effect size estimation was limited by measurement error in key variables. We measured personality and depressive symptoms indirectly through informant ratings. The somatic symptoms scale derived from the HRS-D was not unidimensional, limiting its scaling properties. We measured cognitive impairment by using one brief performance test. We measured chronic conditions only at baseline and did not include conditions that impair mobility (e.g., joint dysfunction or fractures).

Second, the longitudinal vector consisted of only four widely spaced observations, which may not be adequate to characterize temporal patterns in depressive symptoms. The number of available measurements was further reduced by early study termination caused by participant nursing home placement or death. These adverse events truncated the observations available by nearly one observation per person in 56% of the sample. Because nursing home placement and death were related to age, gender, chronic conditions, and level of cognitive impairment, there were fewer observations to evaluate the relationship between these covariates and depressive symptoms. Finally, because the presence and severity of depressive symptoms were based on observations during the month preceding each clinical evaluation, events occurring in the gaps between annual evaluations were not captured. Thus, it is possible that these data underestimate an individual’s propensity for depressive symptoms during the study period.

Third, this study did not evaluate other potential risk factors for depressive symptoms. These unmeasured covariates include family history (Pearlson et al., 1990; Strauss & Ogrocki, 1996) and neuropathological characteristics (Forstl et al., 1992; Zweig et al., 1989), which are associated with depressive symptoms in persons with AD. Characteristics of the physical and social environments may also affect the rate of depressive symptoms. If depressive symptoms in persons with AD stem from a diathesis-stress process, environmental stresses may trigger depressive symptoms in those who are susceptible as a result of lifelong and disease-related risk factors.

The final set of limitations of this study stem from the use of a prevalent disease cohort derived from a dementia clinic. This source permitted rapid enrollment of a large number of persons.
with the clinical diagnosis of AD based on structured evaluations. However, selection factors related to service utilization may limit the generalizability of the findings. For example, persons with more extreme clinical symptoms are more likely to come to medical attention (Ross et al., 1997). These selection factors are most likely to affect baseline distributions, but they may have less impact on rates of change based on longitudinal measurement of disease characteristics. The wide range of disease severity at baseline may also have considerable effect on the assessment of premorbid personality. Because these retrospective ratings require extrapolation across the length of the disease, demand on the informant’s memory is likely to be greater in persons with more advanced disease.

Future Directions

Depressive symptoms are one component in a broad spectrum of changes in emotion that accompany AD. Our results highlight the potential value of longitudinal studies to quantify these changes over time in relation to other disease characteristics. To date, the focus of research has tended to be on negative emotional states because of their potential impact on family caregivers. However, analyses of positive emotion are also needed to provide a more complete picture of temperament in this disease.

Data from the present study highlight the potential clinical utility of assessing the personality dimension of neuroticism as a predictor of subsequent episodes of negative emotion. However, the heuristic value of personality may extend beyond associations with emotional expression. Empirically grounded theories of neuroticism and extraversion (e.g., Eysenck, 1967) may yield viable hypotheses. For example, does the sensitivity to aversive stimuli systematically change over the course of AD to produce a disproportionate negative emotional response? Does the physical and social environment contribute to individual differences in emotion? As a first step, more detailed longitudinal studies of critical personality dimensions and patterns of emotional responses are needed. To further minimize the potential for bias in informant ratings of premorbid personality, researchers must focus on persons in the early stages of AD.

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