BENEFIT OF PHONEMIC CUEING IN ALZHEIMER'S DISEASE PATIENTS' NAMING PERFORMANCE: BASELINE CORRELATES AND PREDICTIVE UTILITY

A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

By

Brittany Cerbone

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ABSTRACT

Word-finding difficulty, especially when confronted with naming items, is a well-known problem that many individuals with Alzheimer's disease (AD) encounter. The use of neuropsychological measures, imaging technology, and genetic research has all contributed to the understanding of naming deficits in AD and the underlying cognitive processes involved. The effects of providing cues during confrontation naming tasks have also been studied, and research has suggested overall benefits of phonemic cueing. This research project further investigated the benefits of phonemic cueing cross-sectionally and longitudinally among a large sample (N = 1104) of individuals with mild to moderate AD. Cross-sectionally, the study examined neuropsychological and socio-demographic correlates of phonemic cueing benefit, as well as potential modifying effects of genetic vulnerability and dementia severity. Longitudinally, the study determined whether phonemic cueing benefit predicts rate of decline on several dementia severity measures. Results indicated that, consistent with previous literature, mild AD subjects benefited from phonemic cues significantly more than moderate AD subjects. Individuals with higher premorbid IQ were found to benefit more from phonemic cueing, which was expected given research findings on the effects of education on cognitive reserve. Women and men were comparable in overall confrontation naming ability, which contradicted current literature, and women were found to benefit more than men from phonemic cues. Confrontation naming ability accounted for the observed inverse relationship between age and phonemic cueing benefit. Observed differences in PCI between carriers and noncarriers of the ApoE ε4 allele were also accounted for by confrontation naming ability, with carriers performing better on naming tasks compared to noncarriers. Phonemic cueing benefit uniquely contributed to baseline cognitive performance on some semantic measures, phonemic fluency, and one non-semantic visuospatial task. Only lower levels of baseline dementia severity and older age predicted less cognitive impairment at 2-year follow-up.

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Introduction

Confrontation naming deficits and general word-finding difficulties are a well-established issue that many patients with Alzheimer's disease (AD) experience. There is general consensus on the nature and pattern of AD patients' naming difficulties across levels of dementia severity, but there is less clarity on the underlying cognitive processes. Generally, researchers have attributed these deficits to progressive breakdown of semantic networks in the brain, while others have emphasized a lexical access component. Yet, some researchers do not believe that these hypotheses need to be mutually exclusive, and instead propose that both semantic and lexical access disruption can be contributing factors to clinical deficits. The effects of phonemic cueing on the ability to successfully name target words during confrontation naming tasks such as the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) have supported a lexical access component. Due to the heterogeneity of Alzheimer's disease, individuals may differ in the extent of their benefit from phonemic cueing, and this in turn may be associated with a number of variables, such as socio-demographics, genetics (i.e., ApoE genotype), dementia severity, rate of cognitive decline, and neuropsychological functioning. This study will explore the effects of phonemic cueing benefit on confrontation naming in AD cross-sectionally and longitudinally, and will discuss how these results potentially impact our understanding of underlying cognitive processes.

Background Literature on the Nature and Progression of Naming Deficits in AD

Visual naming measures such as the Boston Naming Test have been extremely useful in understanding the nature, progression, and underlying processes involved in word-finding difficulties in AD, and a considerable body of research has been conducted utilizing these neuropsychological measures. A number of studies have explored the types of errors made during naming tasks, the type of profile that AD patients tend to display based on the proportion of error types, how this profile changes as the disease progresses, and factors that may influence performance.

Error types can be separated into approximately six different groups: semantically related, circumlocution, semantically unrelated, phonemic, pure anomia, and visual (Silagi, Bertolucci, & Ortiz, 2015). Semantically related errors occur when a target word is substituted by another word that is related in meaning or category (e.g. sheets for pillows). Some studies may additionally specify whether a semantic error is superordinate to the target word (e.g. "animal" for dog). A circumlocution is a description of the target word's meaning or use (e.g. for mask, "it is used to go to a party"). Unrelated semantic errors occur when a word unrelated in meaning or category is used to substitute for the target word (e.g. camel for pen). Phonemic errors occur when phonemes or syllables are substituted, added, or omitted (e.g. funnel and tunnel). If one fails to give a response or has no name to provide, then this is considered pure anomia. Lastly, visual errors occur when a word is given that is visually similar to the target word (e.g. triangle for pyramid).

Many studies have shown that types of errors made during naming tasks in those with AD tend to primarily be semantically related or superordinate (Barbarotto, Capitani, Jori, Laiacona, & Molinari, 1998; Bayles & Tomoeda, 1983; Chenery, Murdoch, & Ingram, 1996; Martin & Fedio, 1983; Silagi et al., 2015). In addition, the pattern and proportion of error types typically change as the disease progresses. Bayles and Tomoeda (1983) found that those with more severe impairment were more likely to make errors that were semantically unrelated to the target word. Silagi et al. (2015) found that pure anomia responses increased with severity, and that the patients with moderate AD had more variable patterns of errors, including visual errors, compared with the mild group. Barbarotto et al. (1998) discovered that as the disease advanced in severity, the proportion of lexical-semantic types of errors declined, and the proportion of empty and unrelated responses increased, and visual errors were still a minority. Thus, one can deduce that as the disease worsens, the underlying processes involved in object naming are increasingly compromised (Chenery et al., 1996).

Phonemic Cueing Benefit in AD

During the administration of the BNT, if a subject is unable to spontaneously name an object, there are two types of cues that can be provided: semantic and phonemic. The semantic cue is only given in instances that the subject misperceives the item (e.g. calling a pretzel a snake), and therefore the purpose of the semantic cue is to reorient the subject by providing a hint (e.g. "We eat it"). If the response following the stimulus cue is incorrect, the phonemic cue is given (e.g., "The word begins with the sound 'pre'"). The phonemic cue is also given after a failure to respond or after any other incorrect response.

Although the literature on phonemic cueing in confrontation naming is limited, research suggests its benefit in AD patients. Several studies have shown that providing a phonemic cue following the inability to spontaneously name an item significantly helped AD patients retrieve words, on average (Balthazar, Cendes, & Damasceno, 2008; Nebes, 1989; Neils, Brennan, Cole, Boller, & Gerdeman, 1988; Martin & Fedio, 1983). Martin and Fedio (1983) studied 14 mild AD subjects and found that after subjects were given a phonemic cue on the BNT, they correctly named the items about 60% of the time. But, the extent of benefit reported in this study should be interpreted with caution because of factors such as small sample size, younger age than is representative of an AD population (mean age = 58 years), and lack of consideration of education.

The methods and findings of Neils et al. (1988) are more representative of what the current study will investigate. This study examined phonemic cueing using the BNT across 21 AD patients of varying levels of dementia severity. Neils et al. measured the extent of phonemic cueing benefit by calculating a ratio of successful responses to phonemic cues to total number of phonemic cues provided, which is the method by which the present study will operationalize phonemic cueing benefit. It was found that on average, patients provided the correct response for 34.2% of the items on which they were given phonemic cues (SD = 25.8). Overall naming performance moderately correlated with percent benefit from phonemic cues ($r = .53$, $p < .05$). Dementia severity was also found to be moderately correlated with phonemic cueing benefit ($r = -.67$, $p < .05$). Although these results demonstrated the value of phonemic cueing to AD patients, the study's conclusions are limited due to small sample size and limited scope of investigation of the correlates of cueing benefit.

Balthazar et al. (2008) studied phonemic and semantic cueing helpfulness among mildly demented AD patients, individuals with amnestic mild cognitive impairment (aMCI), and healthy controls (n = 16) using the BNT, and found that although the mild AD group needed considerably more cues, and performed significantly worse than aMCI and normal individuals on spontaneous naming, their naming performance was significantly enhanced when provided a phonemic cue, benefiting on average on 37% of the items. Semantic cueing was found to be not as useful, with mild AD individuals benefiting on average on about 22% of the items cued. In addition, after semantic cues were provided, there was still a significant difference between the mild AD group and the other two groups, but when phonemic cues were provided, there was no longer a significant difference in performance between the three groups. Balthazar et al. accounted for age and education, but similar to most other phonemic cueing studies, the sample size was quite small.

Lin et al. (2014) reported similar BNT findings in a larger sample size (n = 104) of mildly to moderately demented AD participants, finding that phonemic cues aided correct name retrieval on 25% of cued items, compared with only an 11% benefit in response to semantic cues. In addition, the AD group's extent of benefit with semantic cues was significantly lower compared to matched controls (n = 115), but was equivalent with phonemic cueing. It is noteworthy that this study, unlike others, utilized ANCOVA to adjust for age, education, and MMSE (Folstein, Folstein, & McHugh, 1975) when examining group differences. In summary, studies on phonemic cueing suggest significant and meaningful benefit for AD patients, especially those who are mildly demented.

Underlying Cognitive Processing Hypotheses for Confrontation Naming Deficits in AD

The processes underlying the deficits in object naming are not well understood, but the most accepted hypothesis for naming difficulty in AD is related to a breakdown in semantic memory (Bayles & Tomoeda, 1983; Bayles & Tomoeda, 1990; Hodges, Salmon, & Butters, 1992; Chertkow & Bub, 1990; Tippett & Farah, 1994). It is suggested that the degenerative nature of the disease leads to progressive damage to semantic memory areas that store knowledge about words and their meanings, and therefore, the inability to name the object is due to the progressive loss of knowledge of that object's attributes that eventually spreads to loss of knowledge of the overall category. The primary source of evidence for this hypothesis relates to the semantic nature of the naming errors made during confrontation naming, discussed earlier. Some studies have also provided support for loss of semantic knowledge by showing consistency in the inability for AD individuals to correctly retrieve a target word across tasks of confrontation naming and object recognition, category fluency (Huff, Corkin, & Growden, 1986), definitions, sorting, word-picture matching (Hodges et al., 1992), and multiple-choice (LaBarge, 1992).

Alternatively, the studies discussed earlier on phonemic cueing provide evidence for a "lexical hypothesis," which is based on the notion that naming difficulties in AD are a result of lexical access and retrieval deficits (Nebes, 1989, Tippett & Farah, 1994), rather than semantic breakdown. Yet, several authors have suggested that an integration of lexical and semantic hypotheses may be necessary to fully understand the complexity of neurodegeneration of brain areas involved in the naming process in those with AD. Neils et al. (1988) suggested that in milder stages of the disease, retrieval deficits primarily accounted for naming deficits, but at moderate and severe stages of the disease, semantic knowledge was particularly compromised and retrieval was not helped by phonemic cueing. Similarly, Balthazar et al. (2008) suggested that in the mild stage of AD, lexical access might play a larger role in naming deficits compared with loss of semantic knowledge, and that naming deficits are likely to be explained by a combination of factors, including loss of semantic knowledge, impaired lexical access, and disrupted attentional processes. LaBarge (1992) also noted that as naming responses become less semantically related and are lacking in content, which is typically associated with more advanced impairment, compromise to semantic structures are more likely and one cannot simply attribute impairment to a breakdown in lexical processing. In summary, semantic breakdown and lexical access impairment do not need to be mutually exclusive and the extent to which each contribute to naming impairment may depend on factors such as disease severity and heterogeneity within AD. The present study will be exploring the extent to which phonemic cueing benefits patients across different levels of dementia of severity.

Neuroanatomical and Functional Correlates of Confrontation Naming in AD

Although this study will not be directly investigating neuroanatomical and functional correlates through neuroimaging, it is appropriate to briefly discuss the literature on brain areas associated with confrontation naming performance in AD. Studies using voxel-based morphometric (VBM) analyses of MRI scans have generally shown correlations between impaired naming performance and cortical thinning of the left temporal lobe, particularly the anterior (Domoto-Reilly, Sapolsky, Brickhouse, Dickerson, & Alzheimer's Disease Neuroimaging Initiative, 2012) and lateral (Grossman et al., 2004) portions. In addition, a longitudinal study by Arlt, Spies, Lehmbeck, and Jahn (2013) found that in mildly demented AD patients, there was a very high correlation ($r = .90$) between rate of BNT point loss per year and the rate of gray matter volume (GMV) loss in the left hippocampus. It should be noted that Arlt et al.'s (2013) longitudinal study did not examine phonemic cueing, and that the current study will investigate if phonemic cueing benefit predicts rate of decline in mildly and moderately demented AD on several cognitive measures.

Melrose et al. (2009) utilized fludeoxyglucose (FDG)-PET scans in a study of AD patients naming of BNT items, and it was discovered that there was bilateral hypometabolism in the inferior temporal lobes of those who had poorer ability to spontaneously name objects. When a phonemic cue was provided, those who successfully named the object after the cue had more metabolic activity in the bilateral inferior frontal gyrus (IFG) and left temporal cortex. These results suggest that when phonemic processes are used to retrieve a word, the brain uses more frontal/executive functions, and it also suggests that naming difficulties in AD are due to deficits in both the temporal-based semantic knowledge network and the frontal-based retrieval processes. Phonemic cueing during picture naming can potentially be linked in this way to tests of letter (or phonemic) fluency and category fluency, which will be discussed more in depth later.

Lastly, Leuzy et al. (2012) analyzed amyloid PET imaging in relation to BNT performance among aMCI and mildly demented AD patients. They found an association between deficits in naming ability and amyloidosis in the bilateral base of the temporal lobe. This suggests that naming deficits are associated with beta-amyloid build-up and synaptic dysfunction in specific areas of the brain, which are both known to increase in magnitude as symptoms of the disease worsen.

Confrontation Naming and Demographic Variables in AD

Research has suggested that women perform significantly worse than men of similar AD severity on confrontation naming tasks, even after controlling for age and education (Buckwalter, Rizzo, McCleary, Shankle, Dick, & Henderson, 1996; Henderson & Buckwalter, 1994; McPherson, Back, Buckwalter, & Cummings, 1999; Randolph et al., 1999; Ripich, Petrill, Whitehouse, & Ziol, 1995), although rate of decline in naming performance was found to be similar in men and women (Hebert et al., 2000; Ripich et al., 1995). The possible reasons as to this observed effect of sex on confrontation naming ability is unclear. Some studies interpreted these results as reflective of greater language impairment in women with AD, while Randolph et al. suggested that the tendency for women to perform worse than men may be a result of BNT item bias favoring men. In addition, Randolph et al. found that the magnitude of differences in naming performance between men and women was similar in both AD subjects and normal controls, which further suggests that the gender effect may not be due to differential language impairment in women with AD. Age has also been shown to have a significant influence on BNT performance in AD, with those who are older tending to perform worse (MacKay, Connor, & Storandt, 2005; Randolph et al., 1999). MacKay et al. also found a similar inverse relationship between age and BNT performance in cognitively normal older adults, and therefore suggested that the observed relationship between age and confrontation naming ability may be due to the cognitive aging process rather than the dementia process. To date, there is no published literature on the possible effects of age and sex on phonemic cueing benefit in AD. Therefore, this study will examine the effects of these demographic variables on overall BNT naming performance and phonemic cueing benefit.

Genetic Risk and Confrontation Naming in AD

One particular gene of interest in Alzheimer's disease is the apolipoprotein E (ApoE) gene on chromosome 19. The ε4 allele variant has been associated with higher risk of developing Alzheimer's disease (Corder et al., 1993; Strittmatter et al., 1993). In neuropsychological studies, this genotype has been studied in those with AD to see how this risk factor may affect cognition (e.g., Lehtovirta et al., 1996; McGuinness, Carson, Barrett, Craig, & Passmore, 2010). Yet, there is very limited research on the possible effects of ApoE genotype on confrontation naming ability in those with AD. Two studies interestingly found, among those with AD, that ε4 *non*-carriers had poorer performance on naming tasks compared with ε4 carriers (van der Vlies et al., 2007; Wolk et al., 2010). In addition, Wolk et al. found that non-carriers had greater frontoparietal atrophy and carriers had greater medial temporal lobe (MTL) atrophy, which the authors suggest underlie the differing clinical phenotypes in naming and other cognitive abilities. In contrast, Miller et al. (2005) studied performance on the BNT among cognitively normal older adults at higher genetic risk for AD, defined here as having a family history of AD and/or one or more ApoE ε4 alleles, and it was discovered that genetic risk was associated with lower BNT scores at baseline and follow-up. Wierenga et al. (2010) found that ApoE ε4 carriers had more widespread brain activity during word retrieval tasks compared with controls, which may suggest the use of compensatory mechanisms.

Overall, these seemingly conflicting results between preclinical and clinical AD populations of the effects of genetic vulnerability on naming ability could suggest that brain areas and cognitive processes may be differentially affected before and after symptoms begin. To date, there is no published literature on the effects of ApoE ε4 on phonemic cueing benefit in those with AD, although a poster by Benge, Massman, Jenkins, Thornton, and Doody (2006) reported that, on average, ApoE ε4 carriers benefited more than ApoE ε4 non-carriers from phonemic cueing over a period of 24 months. This study will explore how the number of ApoE ε4 alleles potentially moderates BNT phonemic cueing benefit.

Confrontation Naming and other Neuropsychological Measures in AD

Premorbid Intellectual Functioning

Neuropsychological tests such as the National Adult Reading Test (NART; Nelson & O'Connell, 1978) and the American version (AMNART; Grober & Sliwinski, 1991) are commonly used to measure estimated premorbid verbal intellectual functioning in those with dementia, since research (e.g., McGurn et al., 2004) has shown that the ability to read irregular words is relatively preserved and not significantly compromised by neurodegeneration (at least in the milder stages of dementia). Pavlik, Doody, Massman, & Chan (2006) found that AMNART was a better predictor than years of education of baseline cognitive performance and rate of cognitive decline. Since educational level is believed to influence the clinical phenotype and progression of AD (Stern, Albert, Tang, & Tsai, 1999), including confrontation naming performance (Randolph, Lansing, Ivnik, Cullum, & Hermann, 1999), and enhance resilience to the pathophysiological effects of the disease (Stern, 2009), then measures of premorbid intellectual functioning can also have implications for cognitive reserve. In fact, Alexander et al. (1997) found that higher premorbid intellectual functioning was associated with greater pathophysiological effects of AD among those of similar severity levels, which the author suggests is in support of a cognitive reserve hypothesis. Although there has been much research on premorbid IQ and AD, little is known about how premorbid IQ may influence specific aspects of language functioning in AD patients. Based on the literature described above, it would be appropriate to hypothesize that factors such as premorbid IQ can significantly influence performance on not only confrontation naming but also on the benefits of phonemic cueing. Perhaps those with higher AMNART scores may benefit more from phonemic cueing and have more resilient semantic ability, which could be indicative of higher cognitive reserve processes. This study will examine the effect AMNART has on phonemic cueing benefit at baseline, while controlling for dementia severity.

Semantic Fluency and Verbal Functioning

Generally, researchers have found that AD patients are better at retrieving words during letter fluency tasks compared with semantic fluency tasks (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Martin & Fedio, 1983; Monsch et al., 1992; Monsch et al., 1994; Troster, Salmon, McCullough, & Butters, 1989), and that letter fluency declines at a slower rate than category fluency (Salmon, Heindel, & Lange, 1999). Using voxel-based lesion symptom mapping (VLSM), deficits in letter fluency were found to be associated with left frontal cortex lesions while deficits in category fluency were associated with left temporal cortex lesions (Baldo, Schwartz, Wilkins, & Dronkers, 2006). Melrose et al. (2009) also showed that poor performance in semantic fluency tasks was associated with hypometabolism in both temporal and IFG regions, whereas poor performance in phonemic fluency was associated with hypometabolism in only the left IFG regions. Relating this to the findings discussed earlier about more frontal/executive processes involved in successful word retrieval after phonemic cueing, it is plausible to hypothesize that phonemic cueing benefit not only would be associated with better performance on semantic fluency tasks, but also with phonemic fluency and executive function tasks.

Research on the relationship between confrontation naming and semantic functioning measures is very limited. Martin and Fedio (1983) found non-significant, yet moderately sized, correlations between BNT total score and WAIS-R Vocabulary ($r = .48$) and WAIS-R Similarities ($r = .39$), which could be due to insufficient power to detect significant effects among a small sample size (N = 14) of patients. Bschor, Kuhl, & Reischies (2001) and Huff et al. (1986) found significant, high correlations between confrontation naming test performance and semantic fluency among varying levels of AD severity ($r = .73$, $p < .01$ and $r = .79$, $p < .001$, respectively). Since it can be hypothesized that those who benefit more from phonemic cueing may have more intact semantic areas, then it can also be hypothesized that phonemic cueing benefit is related to performance on other semantic measures.

In summary, this study will examine the relationship between phonemic cueing benefit and semantic measures such as the WAIS verbal subtests and semantic fluency. It is hypothesized that phonemic cueing benefit will be positively and more strongly associated with performance on semantic measures compared with non-semantic measures (e.g. visuospatial ability, nonverbal memory and word recall, or processing speed), and that due to evidence of more frontal brain processes involved in phonemic cueing, it will also be more strongly associated with verbal fluency and executive function measures.

Relationship Between Naming and Dementia Severity Cross-Sectionally and Longitudinally

As discussed earlier, some researchers have suggested that there is an inverse relationship between phonemic cueing benefit and dementia severity (Balthazar et al., 2008; Neils et al., 1988). Therefore, this study will hypothesize that those with mild dementia will benefit more from phonemic cueing compared to those with moderate dementia.

Longitudinal research on naming and dementia severity has yielded mixed results. Rasmussen et al. (1996) studied predictors of cognitive decline over time, as measured by decline in MMSE score, in a longitudinal cohort consisting of mildly to moderately demented AD participants, and found that better performance on the BNT predicted more rapid decline in MMSE over a 6-month interval. Boller et al. (1991) found that the BNT was the strongest language task predictor of group membership among AD individuals who were classified as either fast decliners or slow decliners, also based on their rate of change in MMSE, but in contrast to Rasmussen et al., poorer performance on the BNT predicted more rapid decline. Other research has found there to be no difference in baseline BNT performance between rapid and slow decliners on the MMSE (Atchison, Bradshaw, & Massman, 2004; Seidl & Massman, 2015). To date, there is no published literature on the predictive power of phonemic cueing benefit and rate of cognitive decline in AD. The present study will investigate if phonemic cueing benefit predicts rate of decline in mildly and moderately demented AD patients on several measures.

Hypotheses

Hypothesis 1: Assessing phonemic cueing benefit based on dementia severity.

Based on existing literature suggesting that those with AD who are milder in severity may have lexical access retrieval deficits and benefit more from phonemic cues, it is hypothesized that mild AD individuals will benefit more from phonemic cues than moderate AD individuals.

Hypothesis 2: Assessing confrontation naming ability and phonemic cueing benefit based on sex.

Prior research has suggested that women tend to perform worse than men of similar AD severity on confrontation naming tasks, although to date, there is no literature on the effects of sex on phonemic cueing benefit. This study hypothesizes that women will perform worse on confrontation naming tasks and phonemic cueing benefit compared to men.

Hypothesis 3: Assessing the relationship between premorbid intellectual functioning and phonemic cueing benefit.

This study hypothesizes that premorbid IQ will positively correlate with phonemic cueing benefit, since it is expected that, similar to education, individuals with higher premorbid IQ will have greater cognitive reserve.

Hypothesis 4: Assessing the relationship between age and phonemic cueing benefit.

To date, there is no literature on the relationship between age and phonemic cueing benefit, although research has shown an inverse relationship between age and confrontation naming ability. This study hypothesizes that age and phonemic cueing benefit will similarly be inversely correlated.

Hypothesis 5: Assessing confrontation naming ability and phonemic cueing benefit based on the number of ApoE ε4 alleles.

Research on genetic vulnerability in AD has generally shown that carriers of the ε4 allele perform better on confrontation naming tasks and phonemic cueing compared to non-carriers. Therefore, this study hypothesizes that phonemic cueing benefit will significantly increase as the number of ε4 alleles increases.

Hypothesis 6: Examining the relationship between phonemic cueing benefit and baseline neuropsychological measures.

Confrontation naming ability has been shown to moderately correlate with semantic measures, and research on phonemic cueing benefit has suggested an association with both phonemic fluency performance and greater frontal brain activation. Therefore, it is hypothesized that phonemic cueing benefit will correlate with semantic measures because of relatively more intact semantic areas, and that it will correlate with tasks involved with frontal brain processes, including phonemic fluency and executive function measures.

Determining whether phonemic cueing benefit predicts rate of cognitive decline.

There is limited, conflicting AD literature on confrontation naming ability performance and rate of cognitive decline, and no published literature to date on the predictive power of phonemic cueing benefit and rate of cognitive decline. Therefore, this study will explore the extent to which phonemic cueing benefit, confrontation naming ability, premorbid IQ, age, and baseline dementia severity predict rate of cognitive decline at 2 years post-baseline.

Methods

Participants

This study consisted of probable AD participants enrolled in a longitudinal study at the Baylor Alzheimer's Disease and Memory Disorder Center (ADMDC). This archival database is approved by the Baylor Institutional Review Board and has also received approval from the University of Houston Committee for the Protection of Human Subjects (UH CPHS). Participants were administered a comprehensive neuropsychological battery that was repeated approximately every year, and ApoE ε4 status was obtained at the baseline evaluation. All participants in the study met diagnostic criteria for probable AD (McKhann et al., 1984) at every time point throughout study participation, including at baseline. Exclusion criteria included non-English speakers (see "Quality Control" results), a diagnosis other than probable AD at any time point, an MMSE score at baseline below 11, and those who either did not have BNT data available, or who had a raw BNT score above 50. This raw score cut-off was designated so that included participants did display evidence of naming difficulty and were administered a sufficient number of phonemic cues to yield meaningful phonemic cue benefit index values. As a result of not all participants returning for follow-up evaluations (primarily due to difficulties traveling to Houston from distant locations), the sample sizes for the follow-up visits are smaller than that of the baseline evaluation.

Before exclusion criteria were applied, the original dataset included 1330 subjects. 13 subjects were excluded because they did not have baseline (e.g. Visit 1) data available. Participants with baseline BNT total score (uncued) of greater than 50 (176 subjects) were removed based on that exclusion criterion. Twenty-eight subjects were excluded whose baseline MMSE score less than 11. One subject was excluded whose baseline MMSE was

"99" (e.g. missing), since inclusion criteria required a baseline MMSE score. Eight non-English speakers were removed, since "Quality Control" results (see below) suggested that there might be differences in confrontation naming and phonemic cueing benefit performance compared to English speakers. After applying inclusion and exclusion criteria, 1104 subjects remained in the database for cross-sectional data analysis. For the longitudinal analysis, 863 subjects who did not have a follow-up visit within 24 months of baseline (+/- 3 months) were excluded. After this exclusion criterion was applied, 241 subjects remained in the database for longitudinal analysis.

Measures

Selected measures from the Baylor ADMDC standard neuropsychological battery were used to test research hypotheses. Participants were administered these tests at baseline evaluation and at all subsequent annual follow-ups (except for the AMNART, which was only administered at baseline).

Cognitive Status and Premorbid Intellectual Functioning:

Mini Mental State Exam (MMSE). The MMSE (Folstein, Folstein, & McHugh, 1975) is a 30-point brief screening instrument for dementia, measuring orientation, memory, language, mental manipulation, and visuoconstruction. For the purposes of this study, the MMSE will be used as an estimate of dementia severity. A cut-off score of 20 will discriminate between mild and moderate dementia.

Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog). The ADAS-Cog (Mohs et al., 1997) is a measure of dementia severity that is widely used in clinical trials for Alzheimer's disease. Subtests include word recall, naming objects and fingers, responding to basic commands, drawing figures, completing steps involving sending a letter, assessment of orientation to time and place, word recognition, and assessment of language ability (including expression, comprehension, and word finding difficulty). Scores range from 0 to 70, with higher scores indicating more impairment.

Clinical Dementia Rating- Sum of Boxes (CDR-SB). The CDR (Morris, 1993) is a measure of six categories of functioning, which include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Information is obtained in the form of a semi-structured interview given separately to patient and informant. The CDR provides a global score of severity, as well as the sum of scores within each category box (CDR-SB).

American National Adult Reading Test (AMNART). The AMNART (Grober & Sliwinski, 1991) is a reading test that estimates premorbid verbal intellectual functioning. Subjects are asked to pronounce 45 irregularly spelled words of increasing difficulty. An algorithm that incorporates both the AMNART error score and years of education yields an estimated premorbid verbal IQ score.

Verbal Measures:

Boston Naming Test (BNT). The BNT (Kaplan, Goodglass, & Weintraub, 1983) is a measure of semantic memory, confrontation naming, and word retrieval ability. The subject is provided 60 line drawings of objects of increasing difficulty one at a time and is asked to provide the name for that object. If unable to spontaneously name it, the subject is provided semantic and/or phonemic cues as necessary. Each correctly named item is one point, with total possible raw score of 60. The BNT total score includes only correct responses given spontaneously or after a stimulus cue. This BNT total score ('uncued') will be compared to the BNT score with phonemic cues in order to assess phonemic cue benefit.

WAIS-R/III/IV Similarities. The Similarities subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) is a test of abstract verbal reasoning in which subjects are asked to identify similarities between two words. Each item is scored zero to two points with higher raw scores indicating better performance. Age-scaled scores were utilized in data analyses.

WAIS-R/III Vocabulary. The Vocabulary subtest of the WAIS-R/III (Wechsler, 1981, 1997) is a test of semantic knowledge in which subjects are asked to define words of increasing difficulty. Each item is scored zero to two points with higher raw scores indicating better performance. Age-scaled scores were utilized in data analyses.

WAIS-R/III/IV Information. The Information subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) tests one's knowledge of cultural and historical information. Each item is scored zero or one points with higher raw scores indicating better performance. Age-scaled scores were utilized in data analyses.

WAIS-R/III/IV Digit Span Backwards. The Digit Span Backwards subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) assesses working memory, executive functions, and mental manipulation by asking subjects to repeat back a string of numbers in backwards order. The raw score is based on the participant's longest backward span.

Category Fluency (Animals*)*. This test (Rosen, 1980) is designed to measure an individual's ability to spontaneously generate items belonging to a semantic category, in this case animals. Examinees are asked to generate as many items as possible in one minute.

Letter Fluency (FAS). This test (Spreen & Benton, 1969; Spreen & Strauss, 1998) measures the individual's ability to spontaneously generate words that begin with the letters 'F', 'A', and 'S' in 1-min time periods.

WMS-R Logical Memory I (LM-I). The LM-I subtest of the WMS-R (Wechsler & Stone, 1987) is a measure of immediate memory involving free recall of two short stories read aloud to subjects. Each story consists of 25 elements, with each of these being worth one point, yielding a total possible maximum score of 50 points.

Verbal Series Attention Test (VSAT). The VSAT (Mahurin & Cooke, 1996) is a test that measures verbal attentional processes. It consists of several timed tasks, including reciting the alphabet, counting backwards, reciting the days of the week and months of the year in forward and backward order, and verbally alternating number and letter in ascending order (1-A-2-B, etc.). Time to completion is the primary performance measure.

Non-Verbal Measures:

Trail Making Test, Part B (TMT-B). Part B of the TMT (Reitan, 1958) is a measure of set-shifting ability in which the participant is instructed to draw lines connecting numbers and letters in ascending, alternating order (1-A-2-B, etc.). Time to completion is the primary performance measure.

WAIS-R/III/IV Block Design. The Block Design subtest of the WAIS-R/III/IV (Wechsler, 1981, 1997, 2008) tests nonverbal, visual-spatial reasoning. Subjects are asked to assemble colored blocks into a design that is identical to a target design. The subtest is scored based on correctness and time, with higher raw scores indicating better performance. Age-scaled scores were utilized in data analyses.

WMS-R Visual Reproduction I (VR-I). The VR-I subtest of the WMS-R (Wechsler & Stone, 1987) is a test of non-verbal memory that consists of four cards with figures on them of increasing difficulty. The subject is requested to draw from memory each figure after it is presented for 10 sec. VR-I total is based on the sum of points for all four stimuli, with a total possible maximum of 41 points.

Analyses

Defining Phonemic Cueing Helpfulness

A Phonemic Cue Index (PCI) was calculated to assess the extent of benefit from phonemic cueing. The PCI is the ratio between the number of correct responses to phonemic cues and the total number of phonemic cues provided (Neils, Brennan, Cole, Boller, & Gerdeman, 1988). The number of correct responses to phonemic cues is the difference between the BNT total score without phonemic cues ("BNT uncued") and the BNT total score with phonemic cues ("BNT cued"). The number of phonemic cues provided is 60 minus the BNT uncued score. This ratio was then multiplied by 100, so that possible PCI scores ranged from 0 – 100, with increasing numbers indicating more benefit from phonemic cueing. The following equation was used to determine PCI:

$$Phonemic\ Cue\ Index\ (PCI) = \frac{(BNT\ cued - BNT\ uncued)}{(60 - BNT\ uncued)} \times 100$$

Covariates In Analyses

For all analyses, the covariates of MMSE, age, AMNART, and BNT total score were considered. Covariates were included in each analysis if results showed a significant correlation of the covariate with both dependent and independent variables.

Phonemic Cueing Index relationship with Age, Sex, and Severity at Baseline

ANCOVA, with appropriate covariates added, were performed to assess whether there was a significant difference in confrontation naming ability and phonemic cueing benefit between males and females. In order to assess the magnitude of difference between males and females, partial eta squared was computed if ANCOVA was found to be significant.

An ANCOVA was performed to assess whether there was a significant difference in phonemic cueing helpfulness between mildly and moderately demented AD patients, and a correlation was computed between dementia severity measures (MMSE, ADAS-Cog, and CDR-SB) and PCI to assess overall strength of relationship between the variables. For this study, mild AD is defined as having an MMSE >= 20 and moderate AD is defined as having an MMSE < 20.

To determine whether age significantly correlates with PCI, a correlation was performed between age and baseline PCI, partialing out appropriate covariates.

Partial Correlations between Phonemic Cueing Index and Neuropsychological Tests at Baseline

One of the primary aims of this study includes determining whether PCI significantly correlates with various other neuropsychological measures at baseline evaluation. Therefore partial correlations were computed between the baseline PCI and the neuropsychological tests specified under the “Measures” section to assess the relationship between PCI and current cognitive functioning. In addition, this study assessed the correlation between PCI and estimated verbal premorbid intellectual functioning (as measured by the AMNART), partialing out appropriate covariates.

Phonemic Cueing Index and the Number of ApoE ε4 Alleles

To assess whether the number of ApoE ε4 alleles is associated with phonemic cueing benefit and confrontation naming ability at baseline, ANCOVA, with appropriate covariates added, were performed to compare PCI and BNT total scores between patients with zero, one, or two ApoE ε4 alleles.

Phonemic Cueing Index and Predicting Rate of Decline

Another aim of the study is to determine whether PCI performance at baseline predicts subsequent rate of cognitive decline over time. It is beyond the scope of this project to do a mixed effects analysis that would incorporate all longitudinal data, but as a first step, the MMSE, ADAS-Cog total score, and CDR-SB were used as outcome measures to assess dementia severity over a specified time interval of about 2 years (time window of 21-27 months after the baseline visit). For each outcome measure, a multiple regression model that included the predictors of baseline PCI, age, BNT total score, baseline severity measure performance, and AMNART score were evaluated.

Quality Control

The original Boston Naming Test is designed to be administered to English speakers, and therefore it is important to ensure that all participant scores, including those who consider English as a second language (ESL), are a valid reflection of performance. This study examined the comparability of results on the BNT and Phonemic Cueing Index between those who are English speakers and those who consider English to be a second language. If there were significant differences in performance between these two groups, we considered excluding ESL participants from the main analyses.

Due to the administration rule of the BNT to discontinue the test after six consecutive, unsuccessful attempts at naming items, not all participants were administered all items, and thus all possible phonemic cues. However, it is reasonable to presume that participants who discontinued prematurely would not have responded correctly, either spontaneously or with phonemic cues, to remaining items, primarily because items are of increasing difficulty. Nonetheless, as a quality control check, raw BNT protocols from 30 participants of varying dementia severity were randomly selected and manually scored in order to compare the scores to those in the raw database. A crosscheck correlation of 0.9 or above was considered satisfactory for study purposes.

Results

Analyses Utilizing Baseline Sample Data

Quality Control

Of 1112 possible participants, there were eight subjects who were non-fluent in English and 76 subjects who had missing/unknown language fluency information. After adjusting for baseline MMSE, significant differences were found between fluent and non-fluent groups for BNT Total Score with phonemic cues [$F(2,1033) = 5.01$, $p < .05$], and PCI [$F(2,1033) = 3.97$, $p < .05$]. BNT Total Score trended towards significance [$F(2,1033) = 3.54$, $p = .06$]. Analysis of the same language variables between English speakers and those who had unknown language fluency was not found to be significantly different (p's > .05). Therefore, the eight non-English speakers were removed from the final data analysis.

Raw BNT protocols from 30 participants (15 mild AD severity and 15 moderate AD severity) were randomly selected and PCI was manually scored in order to compare results in the raw database. Results showed a crosscheck correlation of $r = .98$ for mild AD subjects and $r = .96$ for moderate AD subjects. Therefore, results were considered satisfactory (i.e., above $r = .90$) for study purposes.

Demographics

Of the 1104 participants with baseline data, 70.0% were female, and 90.8% were Caucasians. The mean age of participants was 75.63 (*SD* = 8.00). Participants had a mean estimated symptom duration of 3.87 years (*SD* = 2.39). Using the MMSE cut-off point of 20 to differentiate AD severity status, 54% of the sample had mild AD at baseline. The average years of education was 13.54 years (*SD* = 3.21). ApoE ε4 status was obtained from 927 participants. Of these, 10.9% ($n = 101$) were homozygous for the allele, 47.6% ($n = 441$) were heterozygous for the allele, and 41.5% ($n = 385$) lacked the allele.

Test performance

Performances on neuropsychological tests were also examined in the entire baseline sample (see Table 1). On the BNT, the 'average' participant got 7 more items correct when given the phonemic cues, providing the correct response on about 32% of the items on which they were given these cues.

To examine whether WAIS subtest scores were comparable in across the different test versions, a one-way ANOVA was performed for each subtest (with test version as the between-subjects factor). As shown in the Appendix, standard scores for the different versions of Similarities, Vocabulary, and Block Design; and longest Digit Span Backwards did not differ significantly, but Information scores did differ ($p < .001$). The WAIS-R Information scores were significantly higher than scores from the WAIS-3 and WAIS-4 versions. After further analysis of partial correlations with PCI (see Hypothesis 6 results), it was decided that combining all three WAIS versions of the Information subtest was acceptable.

Table 1. Baseline Performance on Neuropsychological Tests

Test	Mean (*SD*)	Test	Mean (*SD*)
Baseline MMSE[a] (n = 1104)	20.02 (4.71)	WMS-R LM I[a] (n = 1095)	5.70 (4.63)
AMNART IQ (n = 906)	106.23 (9.84)	WMS-R VR I[a] (n = 1085)	12.93 (8.07)
BNT Total Score (Uncued)[a] (n = 1104)	32.88 (12.34)	WAIS R/3/4 Digit Span Backwards (LDSB)[a] (n = 1095)	3.43 (1.22)
BNT Total Score With Phonemic Cue[a] (n = 1104)	39.65 (13.96)	TMT B[a] (n = 333)	240.21 (76.14)
PCI[a] (n = 1104)	31.84 (21.85)	VSAT[a] (n = 1094)	230.76 (82.98)
WAIS-R/3/4 Information SS (n = 1030)	7.21 (2.73)	ADAS-Cog Total Score[a] (n = 931)	24.86 (10.40)
WAIS-R/3/4 Similarities SS (n = 1029)	6.96 (2.75)	ADAS-Cog Word Recall[a] (n = 938)	7.14 (1.48)
WAIS-R/3 Vocabulary SS (n = 931)	8.56 (2.680)	ADAS-Cog Word Recognition[a] (n = 930)	6.16 (3.17)
WAIS-R/3/4 Block Design SS (n = 999)	6.26 (3.00)	CDR-SB[a] (n = 1015)	6.70 (3.51)
Animals[a] (n = 1020)	7.63 (4.19)	Letter Fluency (FAS)[a] (n = 973)	20.79 (11.55)

Note. [a]Mean raw score is presented.

Examination of Possible Covariates

As mentioned earlier, the covariates of MMSE, age, AMNART, and BNT total score will be considered for partial correlation and ANCOVA analyses of PCI with other variables of interest. Covariates were determined based on significance with the variable of interest at $p < .01$ in order to adjust for multiple comparisons. PCI was found to be significantly associated with all covariates of interest. Table 2 is a summary of correlations between each covariate of interest with the dependent variable (PCI) and various independent variables used in the subsequent partial correlation analyses.

Table 2.
Correlations Between Covariates and Baseline Neuropsychological Test Scores

	Covariates of Interest				
	MMSE	Age	AMNART	BNT Total	Covariates
PCI	.43*	-.15*	.38*	.69*	
MMSE	-	-.07	.33*	.51*	AMNART BNT Total
Age	-.07	-	.04	-.19*	BNT Total
AMNART	.33*	.04	-	.40*	MMSE BNT Total
BNT Total	.51*	-.19*	.40*	-	Age MMSE AMNART
LM I	.56*	-.03	.19*	.40*	MMSE AMNART BNT Total
VR I	.57*	-.05	.22*	.29*	MMSE AMNART BNT Total
VSAT	-.61*	-.08*	-.36*	-.43*	All

	MMSE	Age	AMNART	BNT Total	Covariates
Digit Span Backward	.44*	.13*	.36*	.23*	All
BNT with Phonemic Cue	.51*	-.18*	.42*	.96*	All
WAIS Information	.48*	.05	.48*	.51*	MMSE AMNART BNT Total
WAIS Similarities	.40*	.10*	.43*	.45*	All
WAIS Vocabulary	.39*	.14*	.60*	.44*	All
WAIS Block Design	.49*	.17*	.25*	.22*	All
Animals	.42*	-.03	.14*	.39*	MMSE AMNART BNT Total
FAS	.41*	.04	.41*	.34*	MMSE AMNART BNT Total
TMT B	-.48*	.05	-.28*	-.27*	MMSE AMNART BNT Total
ADAS Recall	-.55*	-.04	-.19*	-.39*	MMSE AMNART BNT Total
ADAS Recognition	-.52*	.13*	-.16*	-.40*	All
ADAS Total[a]	-.75*	.02	-.27*	-.55*	AMNART BNT Total

	MMSE	Age	AMNART	BNT Total	Covariates
CDR-SB[a]	-.66*	.17*	-.22*	-.44*	Age AMNART BNT Total

Note. * $p < .01$, two-tailed. [a] MMSE was not included as a covariate for dementia severity measures.

Covariates were also determined for ANCOVA analyses between PCI and sex, the number of ApoE ε4 alleles, and baseline dementia severity status. Inclusion of covariates were based on statistical significance with the variable of interest at $p < .01$. Table 3 provides a summary of these results below.

Table 3.
Descriptive Statistics of Covariates of Interest and Sex, ApoE ε4 alleles, and Baseline Dementia Severity

		Means (*SD's*) of Covariates of Interest				
		MMSE	Age	AMNART	BNT Total	Covariates
Sex	Men	20.58 (4.90)	74.95 (8.57)	106.81 (10.39)	34.06 (12.45)	MMSE*
	Women	19.78 (4.61)	75.92 (7.73)	105.98 (9.60)	32.38 (12.27)	
ApoE ε4 alleles	0	20.62 (4.85)	77.39 (8.56)	106.21 (9.37)	31.85 (12.81)	Age* BNT Total*
	1	20.31 (4.47)	75.28 (7.34)	106.70 (10.13)	34.54 (11.50)	
	2	19.16 (4.93)	73.78 (6.75)	106.33 (9.16)	35.28 (11.88)	
Dementia Severity	Mild	-	75.39 (7.55)	108.34 (9.59)	37.91 (10.10)	AMNART* BNT Total*
	Moderate	-	75.91 (8.49)	103.12 (9.39)	27.04 (12.14)	

Note. *Significance level = $p < .01$.

Baseline Analysis of Phonemic Cue Index.

Hypothesis 1: Assessing phonemic cueing benefit relationship to dementia severity.

An analysis of covariance was performed to compare phonemic cueing benefit between patients with mild versus moderate dementia severity. Using AMNART as a covariate, results indicated that mild AD individuals benefited significantly more (M = 38.47, SE = 0.84, 95% CI [36.82, 40.12]) from phonemic cueing than those with moderate AD (M = 26.42, SE = 1.03, 95% CI [24.41, 28.43]), $F(2,903) = 79.96$, $p < .001$, $\eta_p^2 = 0.08$.

When BNT total score was added to the ANCOVA analysis as a covariate, the conclusion was comparable, with mild AD individuals benefiting significantly more (adjusted *M* = 35.02, *SE* = 0.70, 95% *CI* [33.66, 36.39]) from phonemic cueing than those with moderate AD (adjusted *M* = 31.51, *SE* = 0.86, 95% *CI* [29.82, 33.19]), $F(3,902) = 9.27$, $p = .002$, $\eta_p^2 = 0.01$. Therefore, one can conclude that those with mild AD severity benefit significantly more from phonemic cues than those with moderate AD severity.

To assess the overall relationship between dementia severity and phonemic cueing benefit, a correlation between PCI and three dementia severity measures (MMSE, ADAS-Cog total score, and CDR-SB). When examining the relationship between MMSE and PCI and ADAS-Cog total score and PCI with only AMNART partialed out, a moderately strong, significant correlation (MMSE: $r = .31$, two-tailed $p < .001$; ADAS-Cog: $r = -.39$, two-tailed, $p < .001$) was found. When BNT total score was added to the partial correlation analysis, although the results were still statistically significant, the effect sizes of the correlations became small (MMSE: $r = .09$, two-tailed $p = .01$; ADAS-Cog: $r = -.11$, two-tailed $p = .001$). For CDR-SB and PCI, with age and AMNART partialed out, a negative, small to medium, significant correlation ($r = -.26$, two-tailed $p < .001$) was found. When BNT total score was added to the analysis, the effect size of the correlation became small but remained significant ($r = -.08$, two-tailed $p = .01$). Therefore, there appears to be a small, overall relationship between dementia severity and phonemic cueing benefit in which increasing dementia severity is associated with decreased phonemic cueing benefit.

Hypothesis 2: Assessing confrontation naming ability and phonemic cueing benefit based on sex.

An analysis of covariance was performed to compare confrontation naming ability and phonemic cueing benefit between men and women. Using MMSE as a covariate, results indicated that women and men performed comparably on BNT total score (Men: $M = 33.32$, $SE = 0.59$, 95% CI [32.17, 34.47]; Women: $M = 32.69$, $SE = 0.38$, 95% CI [31.94, 33.44]), $F(2,1101) = 0.79$, $p > .05$, and on BNT total score with phonemic cues (Men: $M = 39.05$, $SE = 0.66$, 95% CI [37.75, 40.34]; Women: $M = 39.91$, $SE = 0.43$, 95% CI [39.06, 40.76]), $F(2,1101) = 1.19$, $p > .05$. ANCOVA analysis of sex and PCI, with MMSE as a covariate, indicated that women benefited significantly more from phonemic cues ($M = 33.42$, $SE = 0.71$, 95% CI [32.04, 34.81]) than men ($M = 28.13$, $SE = 1.08$, 95% CI [26.02, 30.26]), $F(2,1101) = 16.73$, $p < .001$, $\eta_p^2 = 0.02$. Therefore, men and women performed comparably on overall confrontation naming abilities with or without phonemic cues, but, on average, women benefited significantly more from phonemic cues compared to men.

Hypothesis 3: Assessing the relationship between premorbid intellectual functioning and phonemic cueing benefit.

To assess the strength of relationship between premorbid intellectual functioning and phonemic cueing benefit, a correlation between AMNART and PCI, with MMSE and BNT total score partialed out, was performed. With only MMSE partialed out, a positive, moderately strong, significant correlation ($r = .29$, two-tailed $p < .001$) was found between baseline AMNART and PCI. When BNT total score was added to the partial correlation analysis, the effect size of the correlation became smaller, although the result was still statistically significant ($r = .15$, two-tailed $p < .001$). Therefore, those with higher premorbid intellectual functioning tended to benefit more from phonemic cues.

Hypothesis 4: Assessing the relationship between age and phonemic cueing benefit.

To assess the strength of relationship between age and phonemic cueing benefit, a correlation between age and PCI, with BNT total score partialed out, was performed. Results indicated a statistically non-significant relationship between age and phonemic cueing benefit ($r = -.02$, two-tailed $p > .05$).

Hypothesis 5: Assessing confrontation naming ability and phonemic cueing benefit based on the number of ApoE ε4 alleles.

An analysis of covariance was performed to compare confrontation naming ability and phonemic cueing benefit between participants with zero, one, or two ApoE ε4 alleles. Post-hoc pairwise comparisons using Fisher's LSD test were performed, adjusting for Type I error by using a new critical alpha of $\alpha/3 = .0167$. Using age as a covariate, results indicated that non-carriers had significantly lower BNT total scores ($M = 32.31$, $SE = 0.63$) compared to those with one ($M = 34.33$, $SE = 0.55$) ε4 allele, $p = .016$, omnibus $F(3, 923) = 3.32$, $p < .05$, $\eta_p^2 = 0.01$. ANCOVA analysis of PCI and the number of ApoE ε4 alleles, using age as a covariate, indicated that those who were non-carriers of the ε4 allele benefited significantly less from phonemic cues ($M = 30.41$, $SE = 1.12$) compared to those with one ($M = 34.35$, $SE = 0.98$) ε4 allele, $p < .01$, omnibus $F(3,923) = 4.00$, $p = .02$, $\eta_p^2 = 0.01$. When BNT total score was added as a covariate to the analysis, the overall omnibus and post-hoc pairwise comparisons became non-significant, $F(4, 922) = 1.11$, $p > .05$.

Hypothesis 6: Examining the relationship between phonemic cueing benefit and baseline neuropsychological measures.

Partial correlations were performed between PCI and baseline neuropsychological measures in order to assess the relationship between phonemic cueing benefit and baseline cognition. Results indicated that all verbal neuropsychological measures, with the exception of Digit Span Backwards, and the nonverbal measure Block Design, were significantly correlated with PCI when BNT total score was not partialed out. When BNT total score was partialed out, only Similarities, Vocabulary, Letter Fluency, and Block Design remained statistically significant (all *p*'s < .01, two tailed). The summary of results is provided in Table 4 below.

Since WAIS-R Information scores were found to significantly differ from WAIS-3 and WAIS-4 versions, separate partial correlations were performed comparing the results between PCI and combination versions WAIS 3/4 and WAIS R/3/4 (See Appendix Table 2). When BNT total score was not partialed out, the WAIS Information R/3/4 correlation was significant, but the WAIS Information 3/4 correlation was non-significant. But when BNT total score was partialed out, both Information combinations' correlations were non-significant.

Table 4. Partial Correlations between PCI and Neuropsychological Tests

Test	Pearson's *r* (*r* with BNT partialed)	Test	Pearson's *r* (*r* with BNT partialed)
WAIS-R/3/4 Information SS[b] (n = 865)	.14** (-.02)	WMS-R LM I[b] (n = 903)	.12** (.00)
WAIS-R/3/4 Similarities SS[a] (n = 867)	.27** (.14**)	BNT Total Score[c] (n = 906)	.57** (N/A)
WAIS-R/3 Vocabulary SS[a] (n = 794)	.24** (.12**)	VSAT[a] (n = 903)	-.12** (-.03)
Animals[b] (n = 900)	.18** (.03)	TMT B[b] (n = 322)	-.13 (-.12)
Letter Fluency (FAS)[b] (n = 893)	.14** (.10**)	WAIS-R/3/4 Block Design SS[a] (n = 859)	.09** (.11**)
Digit Span Backwards (LDSB)[a] (n = 900)	.01 (.03)	WMS-R VR I[b] (n = 895)	.05 (.07)

Note. Critical alpha = .01. ** $p < .01$. [a]Age, Baseline MMSE, AMNART IQ, and BNT total score partialed out. [b] Baseline MMSE, AMNART IQ, and BNT total score partialed out. [c] Age, Baseline MMSE, and AMNART IQ partialed out.

Analysis of Longitudinal Sample

Longitudinal sample compared to excluded baseline participants

The participants in the longitudinal sample were compared, on demographics and other factors, to the participants who were in the baseline sample but excluded from longitudinal analysis for failing to meet criteria for inclusion. Independent samples t-tests and chi-square tests were performed, and participants did not significantly differ on sex, age, education, symptom duration, or the number of ε4 alleles. Chi-square analysis yielded a significant difference in baseline AD severity status (using MMSE cut-off scores), with the longitudinal sample having a significantly larger proportion of mild AD severity subjects compared to the excluded sample [χ^2 (2, N = 1042) = 52.42, $p < .001$). In addition, independent sample t-tests revealed significant differences in baseline MMSE [$t(1102) = 8.57$, $p < .001$], AMNART IQ [$t(911) = 2.12$, $p = .03$], BNT total score [$t(1102) = 6.96$, $p < .001$], PCI [$t(1102) = 5.69$, $p < .001$], ADAS-Cog total score [$t(929) = 7.48$, $p < .001$], and CDR-SB [$t(1013) = 6.67$, $p < .001$]. For all significantly different neuropsychological variables, performance was better in the longitudinal sample than in the excluded sample.

Demographics of longitudinal sample

After exclusion criteria were applied, 241 participants remained for longitudinal analysis across baseline and at 2-year follow-up (+/- 3 months). Of these, 66.4% were female, and 93.4% were Caucasian. The mean age of participants was 74.95 (*SD* = 7.36). Participants had a mean estimated symptom duration of 3.77 years (*SD* = 2.14). Using the MMSE cut-off point of 20 to differentiate AD severity status, 74.3% of the sample had mild AD at baseline. The average years of education was 13.77 years (*SD* = 3.25). ApoE ε4 status was obtained from 225 participants. Of these, 10.2% ($n = 23$) were homozygous for the allele, 48.4% ($n = 109$) were heterozygous for the allele, and 41.4% ($n = 93$) lacked the allele.

Test performance of longitudinal sample

Performance on neuropsychological tests at baseline and follow-up were analyzed (see Table 5).

Table 5. Baseline and 2-Year Follow-Up Performance on Neuropsychological Tests			
Baseline	Mean (*SD*)	Follow-Up	Mean (*SD*)
PCI[a] (n = 241)	38.82 (20.87)	PCI[a] (n = 241)	29.38 (22.02)
BNT Total Score (Uncued)[a] (n = 241)	37.67 (10.20)	BNT Total Score (Uncued)[a] (n = 241)	30.67 (13.75)
BNT Total Score (Cued)[a] (n = 241)	45.13 (10.23)	BNT Total Score (Cued)[a] (n = 241)	37.23 (15.48)
MMSE[a] (n = 241)	22.25 (4.03)	MMSE[a] (n = 241)	17.76 (5.58)
ADAS-Cog Total Score[a] (n = 225)	20.47 (7.76)	ADAS-Cog Total Score[a] (n = 231)	29.10 (12.58)
CDR-SB[a] (n = 230)	5.37 (2.68)	CDR-SB[a] (n = 232)	8.98 (4.19)
AMNART IQ (n = 233)	107.35 (10.24)	N/A	
Note. [a]Mean raw score is presented.			

Hypothesis 7: Determining whether phonemic cueing benefit predicts rate of cognitive decline.

Multiple, linear regression was performed to examine whether dementia severity at 2-year follow-up (+/- 3 months) is predicted by baseline phonemic cueing benefit, above and beyond age, AMNART IQ, BNT total score, and dementia severity at baseline. Outcome measures assessing dementia severity included MMSE, ADAS-Cog total score, and CDR-SB at follow-up, and were analyzed separately. Results indicated that baseline PCI did not significantly predict dementia severity at two years post-baseline. Specifically, with MMSE as the dependent variable, baseline MMSE and age were the only significant predictors in the model, such that older age at baseline [β = 0.12, $t(227) = 2.28$, $p < .05$] and higher baseline MMSE scores [β = .64, $t(227) = 11.58$, $p < .001$] predicted higher MMSE scores at follow-up (e.g. lower dementia severity). Overall variance explained in MMSE at follow-up by this model was R^2 (adjusted) = .41, $F(5,227) = 33.04$, $p < .001$. Using the ADAS-Cog total score as the dependent variable, baseline ADAS-Cog, AMNART IQ, and age were the only significant predictors in the model, such that older age at baseline [β = -.14, $t(211) = -2.53$, $p < .05$] predicted lower ADAS-Cog scores at follow-up (e.g. lower dementia severity), higher estimated premorbid IQ [β = .12, $t(211) = 2.14$, $p < .05$] predicted higher ADAS-Cog scores at follow-up (e.g. greater dementia severity), and higher baseline ADAS-Cog scores [β = .63, $t(211) = 10.85$, $p < .001$] predicted higher ADAS-Cog scores at follow-up (e.g. greater dementia severity). Overall variance explained in ADAS-Cog total at follow-up by this model was R^2 (adjusted) = .41, $F(5,211) = 31.00$, $p < .001$. Lastly, using the CDR-SB as the dependent variable, only baseline CDR-SB [β = .48, $t(210) = 7.81$, $p < .001$] was significantly predictive of CDR-SB at follow-up in the positive direction (e.g. greater dementia severity at baseline predicted greater dementia severity at follow-up). Overall variance explained in CDR-SB by this model was R^2 (adjusted) = .28, $F(5,210) = 17.64$, $p < .001$. See Tables 6 – 8 for a full summary of results.

Table 6. Multiple Regression of Baseline Predictors and Dementia Severity (MMSE) at Follow-Up

Predictors	*B*	*SE B*	β	*t*
Constant	-7.38	4.29	-	-1.72
Baseline MMSE	0.89	0.08	.64	11.58*
AMNART IQ	-0.03	0.03	-.06	-1.10
Age	0.90	0.04	.12	2.28*
BNT Total Score	0.06	0.04	.11	1.77
PCI	-0.01	0.02	-.04	-0.62

Note. * $p < .05$. R^2 (adjusted) = .41.

Table 7. Multiple Regression of Baseline Predictors and Dementia Severity (ADAS-Cog Total Score) at Follow-Up

Predictors	*B*	*SE B*	β	*t*
Constant	13.49	10.57	-	1.23
Baseline ADAS-Cog	1.02	0.09	.63	10.85*
AMNART IQ	0.14	0.07	.12	2.14*
Age	-0.23	0.09	-.14	-2.53*
BNT Total Score	-0.05	0.08	-.04	-0.55
PCI	-0.04	0.04	-.07	-1.02

Note. * $p < .05$. R^2 (adjusted) = .41.

Table 8. Multiple Regression of Baseline Predictors and Dementia Severity (CDR-SB) at Follow-Up

Predictors	*B*	*SE B*	β	*t*
Constant	8.04	3.77	-	2.13*
Baseline CDR-SB	0.78	0.10	.48	7.81*
AMNART IQ	-0.03	0.03	-.07	-1.09
Age	0.02	0.04	.03	0.45
BNT Total Score	-0.03	0.03	-.07	-0.94
PCI	-0.01	0.01	-.03	-0.46

Note. $^{*}p < .05$. R^2 (adjusted) = .28.

Discussion

Hypothesis 1

Research findings have suggested that as AD progresses, the underlying processes involved in object naming are increasingly compromised (Chenery et al., 1996), and that dementia severity is significantly correlated with phonemic cueing benefit (Neils et al., 1988). Therefore, it was hypothesized that those with mild AD will benefit more from phonemic cues than those with moderate AD. This hypothesis was supported, even after controlling for overall confrontation naming ability (e.g. BNT total score performance). Using ANCOVA, on average, mild AD subjects benefited from phonemic cueing approximately 35% of the time, whereas moderate AD subjects benefited around 31%. Overall assessment of the relationship between dementia severity and phonemic cueing benefit revealed a small, positive correlation after BNT total score was added as a covariate to the analysis. Therefore, one can conclude that those with mild AD severity benefit, on average, significantly more from phonemic cues than those with moderate AD severity.

Hypothesis 2

To date, there has been no published literature on the possible effects of sex on phonemic cueing benefit in AD, although research has suggested that women tend to perform worse than men of similar AD severity on confrontation naming tasks. Therefore, this study hypothesized that women would benefit less than men from phonemic cueing. The results did not support this hypothesis, or current published literature on sex and confrontation naming ability in those with AD. Results showed that women and men did not differ on overall confrontation naming performance with or without phonemic cues. However, women benefited significantly more from phonemic cues (33%) compared to men (27%), after controlling for MMSE. Possible reasons as to the discrepancy in results compared to published literature could include that previous studies had smaller sample sizes (some less than 100) and did not adopt the present study's inclusion criterion of having an uncued BNT total score of 50 or below. Therefore, the previous samples tended to have higher BNT total score performance and higher MMSE scores compared to the sample in this study, suggesting less overall impairment. Perhaps gender differences in confrontation naming ability become more equalized in those who have greater dementia severity and naming impairment. Since prior studies have not examined sex differences in phonemic cueing benefit, the present study's finding that women of similar AD severity benefit more than men from phonemic cues provides new information to the confrontation naming literature.

Hypothesis 3

Based on existing literature on the effects of education on cognitive reserve (including confrontation naming performance), and research suggesting that estimated premorbid intellectual functioning is a better predictor of baseline cognition than education, it was hypothesized that premorbid IQ would positively correlate with phonemic cueing benefit. Results supported this hypothesis, showing a small, positive correlation between AMNART IQ and PCI once BNT total score was partialed out. Therefore, those with higher premorbid intellectual functioning tend to benefit more from phonemic cues.

Hypothesis 4

Although there is no known existing literature on the relationship between age and phonemic cueing benefit, research has shown an inverse relationship between age and overall confrontation naming performance. This study hypothesized that age and phonemic cueing benefit would similarly be inversely correlated. Results did not support this hypothesis, since the relationship between age and phonemic cueing benefit was no longer found to be statistically significant once BNT total score was partialed out. Age and BNT total score had a negative, small-to-medium relationship, which is consistent with current literature. Therefore, although younger individuals with AD tend to perform better on confrontation naming tasks, they benefit from phonemic cues similarly to that of older individuals with AD. It has been proposed that the relationship between age and confrontation naming ability may be in part due to the cognitive aging process (MacKay et al., 2005). Perhaps these results suggest that the cognitive aging process impacts to a lesser extent the processes involved in phonemic cueing compared to those underlying spontaneous confrontation naming ability, which may point to dissociable underlying cognitive processes.

Hypothesis 5

Research on genetic risk and confrontation naming in AD has suggested that carriers of the ApoE ε4 allele perform better on naming tasks than non-carriers. Although there is no published literature on the effects of ApoE ε4 and phonemic cueing benefit in those with AD, a poster by Benge et al. (2006) found that, across time, carriers benefited more from phonemic cues compared to non-carriers. Therefore, this study hypothesized that ε4 allele carriers would similarly benefit more from phonemic cues compared to non-carriers. The results showed greater phonemic cueing benefit for carriers of one ε4 allele compared to non-carriers only when age was included as a covariate. However, this hypothesis was not ultimately supported once BNT total score was added as a covariate to the analysis, with group differences becoming non-significant. Overall, BNT total score was significantly lower for non-carriers compared to carriers, which is consistent with existing literature. This study had a much larger sample size and compared groups cross-sectionally, which may explain the discrepancy in results compared to Benge et al.'s longitudinal analysis of ApoE ε4 status and phonemic cueing benefit. In addition, Benge et al. reported no significant correlations between baseline BNT total score and PCI change over time, and therefore this variable was not included as a covariate in analyses. Overall, results from the present study indicate that the observed differences in phonemic cueing benefit among carriers and non-carriers in phonemic cueing benefit can mostly be explained by overall confrontation naming ability.

Hypothesis 6

This study hypothesized that phonemic cueing benefit would be positively and more strongly associated with performance on semantic measures compared with non-semantic measures, and that due to evidence of more frontal brain processes involved in phonemic cueing, it would also be more strongly associated with verbal fluency and executive function measures. This hypothesis was partially supported. Without BNT total score partialed out, results showed a significant relationship between PCI and several verbal semantic and fluency measures, as well as one nonverbal measure (Block Design). Once BNT total score was added to the analyses, only Similarities, Vocabulary, Letter Fluency, and Block Design remained statistically significant. Overall, effect size of these relationships was small (*r*'s = .10 to .14). Semantic fluency was no longer found to be significantly related to phonemic cueing benefit once all covariates were included. Executive function measures (e.g. Digits Backwards and TMT B) were not found to be significantly correlated with PCI with or without BNT total score partialed out. It was surprising to find that a nonverbal measure such as Block Design would significantly correlate with PCI, but this relationship was still quite small, and could be anomalous. Overall, results from this study suggest that phonemic cueing benefit is most associated with performance on some semantic measures and letter fluency, and is not related significantly to semantic fluency, executive functions, verbal and nonverbal memory, verbal sustained attention, and general factual knowledge.

Phonemic cueing benefit and prediction of rate of cognitive decline

This study explored whether baseline phonemic cueing benefit significantly predicted cognitive decline at two years post-baseline, as there has been no known literature on this topic to date. Results showed that baseline PCI and BNT total score performance were not predictive of cognitive decline at 2-year follow-up, as measured through MMSE, ADAS-Cog total score, and CDR-SB. Therefore, naming performance does not appear to predict rate of cognitive decline in those with mild to moderate AD. Overall, baseline performance on these dementia severity measures was most predictive of performance at follow-up, which is to be expected. Higher premorbid IQ was found to be a significant predictor of greater dementia severity at follow-up, as measured through the ADAS-Cog total score, which is consistent with some research on the effects of cognitive reserve (e.g. Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996; Scarmeas, Albert, Manly, & Stern, 2006) and inconsistent with other findings (e.g. Fritsch, McClendon, Smyth, & Ogrocki, 2002; Pavlik et al., 2006). Considering that this finding was not replicated with other severity measures, and that the association with ADAS-Cog was small, this finding may be anomalous. Age was also a significant predictor of dementia severity using MMSE and ADAS-Cog as the dependent variables, with older age predicting lower levels of dementia severity at follow-up. This finding is consistent with current literature suggesting that younger individuals with AD, especially those who are considered "early-onset" (e.g. before age 65), tend to decline more rapidly (Bernick, Cummings, Raman, Sun, & Aisen, 2012; Jacobs et al., 1994). Suggested reasons as to this effect of age on cognitive decline include increased plaque burden, greater deficits in cholinergic and monoaminergic neurotransmission, and a greater proportion of atypical, cortical neurofibrillary tangle pathology (relative to hippocampal NTF pathology) in younger-onset AD individuals, which may lead to quicker disease progression (Heii, Yosuke, Kenjii, Takashi, & Reiji, 1992; Ho et al., 2002; Murray et al., 2011). The present study's results closely replicate the findings of Bernick et al., who studied age and rate of cognitive decline in AD using the ADAS-Cog, MMSE, and CDR-SB, and found that older age at baseline was associated with slower decline in ADAS-Cog and MMSE scores over 18 months. Bernick et al. proposed that the non-significant findings on the CDR-SB are possibly due to its greater emphasis on functional change that may not decline fast enough to be captured over a relatively short duration of time, and less sensitivity to age-related differences.

Study Limitations

One study limitation is the exclusion of subjects based on a BNT total score (uncued) greater than 50. This exclusion criterion was used for purposes of clearly identifying individuals who have confrontation naming difficulties and who were offered sufficient opportunities to benefit from phonemic cues. In addition, excluding these subjects would help avoid a ceiling effect. However, this may have resulted in some restriction of range, which could potentially have reduced observed correlations and affected the generalizability of findings, particularly for those in the milder phases of the disease.

A second limitation relates to the administration rules of the BNT to discontinue the test after six consecutive, unsuccessful attempts at naming items. Therefore, some participants, especially those who were moderate in AD severity, were not administered all items. Although one can reasonably presume that those who discontinued prematurely would not have responded correctly to remaining items, one cannot be completely certain about how these individuals would have performed if the whole task were administered. However, the crosscheck quality analysis on a sub-set of moderate AD individuals showed an acceptable correlation (r = .96) between raw database data and raw BNT protocols, which hopefully provides strong support for the validity of scores relating to phonemic cueing benefit across AD severity.

The study sample was very homogenous in terms of race and ethnicity, since 90.8% of the sample was Caucasian and 93.9% was non-Hispanic. Therefore, future studies should focus on whether results replicate in more culturally and racially diverse samples to further understand the extent of generalizability of this study's findings.

The study sought to analyze the relationship among variables with the assumption that these measures "purely" reflect a particular domain (e.g. semantic memory, language, executive functions, visuospatial ability). However, this is oftentimes not the case, as measures rarely reflect only one aspect of cognitive functioning. For instance, although for this study's purposes, Similarities is considered a verbal semantic measure, it can also be considered an executive function measure due to its abstract reasoning component. In addition, sometimes individuals performing visuospatial tasks may utilize verbal strategies to further enhance performance.

A large proportion of individuals were excluded from the longitudinal sample because their follow-up visit was outside of the +/- 3-month window. Therefore, future studies may consider either extending this window of time to increase sample size or utilizing a different method of longitudinal analysis (e.g. mixed effects or latent growth curve modeling) that may better capture performance across time.

Lastly, comparisons of the longitudinal sample to the excluded subjects sample revealed that performance on all neuropsychological variables was significantly better in the longitudinal sample, and that individuals were significantly milder in AD severity. This discrepancy is possibly a reflection of differential attrition of subjects who were moderate in AD severity at baseline, since perhaps they were too impaired to come for a follow-up visit (or were deceased). Therefore, this could potentially skew the results of the regression analysis.

Implications

The aims of this study were to assess phonemic cueing benefit and its relationship with neuropsychological and socio-demographic factors, to determine whether factors such as dementia severity and genetic vulnerability may impact performance, and whether it predicts rate of cognitive decline. The present study sought to provide a greater understanding of the role of phonemic cueing benefit among those with mild to moderate AD and cognitive mechanisms that underlie confrontation naming ability in AD. Key findings were that: 1) Mild AD individuals benefited from phonemic cues significantly more than moderate AD individuals; 2) Individuals with higher premorbid IQ benefited more from phonemic cueing; 3) Although women and men were comparable in overall confrontation naming ability, women benefited more than men from phonemic cues; 4) Confrontation naming ability accounted for the observed relationship between age and phonemic cueing benefit and differences between carriers and noncarriers of the ApoE ε4 allele, with younger individuals and carriers of one ε4 allele performing better on naming tasks; 5) Phonemic cueing benefit uniquely contributed to baseline cognitive performance on some semantic measures, phonemic fluency, and one non-semantic visuospatial task; and 6) Only lower levels of baseline dementia severity and older age predicted less cognitive impairment at 2-year follow-up.

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Appendix

Table 1. Descriptive Statistics and Comparisons of Different WAIS Versions of Subtests

		Means (*SD's*) of WAIS Subtests				
		Information* (N = 1030)	Similarities (N = 1029)	Vocabulary (N = 931)	Block Design (N = 999)	Digit Span LDSB (N = 1095)
WAIS	R	7.48 (2.94) n = 591	7.07 (2.65) n = 610	8.63 (2.71) n = 592	6.14 (2.88) n = 584	3.42 (1.27) n = 656
	3	6.96 (2.30) n = 357	6.85 (2.76) n= 341	8.44 (2.64) n = 339	6.30 (3.04) n = 337	3.42 (1.18) n = 361
	4	6.34 (2.70) n = 82	6.59 (3.32) n = 78	N/A	6.96 (3.62) n = 78	3.56 (1.03) n = 78

Note. *Significance level = $p < .01$. WAIS-R significantly different from WAIS-3 and WAIS-4 at $p < .01$ significance level.

Table 2. Partial Correlations between PCI and WAIS Information Subtest Versions R, 3/4, and R/3/4

Test	Pearson's *r* (*r* with BNT partialed)
WAIS-R Information SS[a]	.22** (.04)
WAIS-3/4 Information SS[b] (n = 893)	.08 (-.11)
WAIS-R/3/4 Information SS[a] (n = 865)	.14** (-.02)

Note. Critical alpha = .01. ** $p < .01$. [a] Baseline MMSE, AMNART IQ, and BNT total score partialed out. [b]Age, Baseline MMSE, AMNART IQ, and BNT total score partialed out.