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Objective: Alzheimer's disease (AD) research typically focuses on memory. However, executive functioning (EF) deficits are also common among AD patients; these deficits are associated with decreased functioning in activities of daily living, an important criterion in diagnosing AD. A classic test of EF ability, the Wisconsin Card Sort Test (WCST), has demonstrated sensitivity to differentiating individuals with AD from healthy controls, discriminating AD

groups based on disease severity, and distinguishing AD from other types of dementia. Such sensitivity to AD raises the possibility that the WCST is also sensitive to very early, preclinical differences between those who have heightened risk for AD and those with lower risks. **Method:** The current study, therefore, examined WCST performance in healthy, cognitively intact older adults with a first-degree (i.e., sibling or parent) family history (FH) of AD (n _ 18) and those with no such FH of AD (n _ 24). **Results:** Results revealed significant group differences for Categories Achieved, Percent Conceptual Level Responses, Total Errors, Perseverative Errors, and Non-Perseverative Errors, with the FH_ group consistently exhibiting poorer performance. Moreover, hierarchical regression analyses indicated that after accounting for age, sex, and education, FH significantly predicted all 5 of these variables. **Conclusions:** These results speak to the potential role of EF in bolstering the current understanding of early cognitive markers of future decline. Furthering what is known about the relationship between AD and nonmemory specific domains of cognition such as executive functioning may allow for better prediction of cognitive decline and potential progression to AD.

Keywords*: Alzheimer's disease, executive function, genetic predisposition to disease, neuropsychological tests, risk factors, predictive value of tests

Early detection of Alzheimer's disease (AD) will be essential for the development and implementation of interventions that can prevent its damaging effects from progressing to produce significant or devastating impairments to quality of life. In the current era of increasing life expectancy, a growing aged population, and heightened AD prevalence (Alzheimer's Association, 2012; 2013), identification of early markers of future decline is indeed urgent. As memory impairment is a hallmark symptom of AD (Clark et al., 2012; Salmon & Bondi, 2009) and deficits in this area are particularly devastating to independence and quality of life (Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sørensen, 2004), AD research has been primarily focused on it. However, memory is not the only cognitive domain to show early decline in individuals who will go on to be diagnosed with AD. As such, examining performance in domains of cognitive functioning beyond memory may provide additional insight into the differentiation between these groups and improve the potential for early detection of AD.

Executive functioning (EF) is one such cognitive domain that has recently received growing attention in the AD literature (Duarte et al., 2006; Espinosa et al., 2009; McGuinness, Barrett, Craig, Lawson, & Passmore, 2010). Indeed, recent diagnostic recommendations from

the National Institute on Aging and the Alzheimer's Association include a specific classification for nonamnestic AD presentations characterized specifically by executive dysfunction (McKhann et al., 2011). EF is an umbrella term used to describe higher order cognitive processes that are critical for engagement in complex thought and behavior (Daniels, Toth, & Jacoby, 2006; Elliott, 2003). It includes abilities such as planning, shifting from one mental "set" to another, updating and monitoring of information, and inhibitory control (Miyake et al., 2000). EF deficits among individuals who have been diagnosed with AD are now widely recognized (Espinosa et al., 2009; Stokholm, Vogel, Gade, & Waldemar, 2006; Takeda et al., 2010). More important, it has been suggested that memory deficits in AD are related to executive impairments (Baudic et al., 2006; Gleichgerrcht, Torralva, Martinez, Roca, & Manes, 2011; Hasher, Lustig, & Zacks, 2007) and that EF deficits are associated with decreased functioning in activities of daily living, which represent an essential criterion in the diagnosis of AD (Jefferson, Paul, Ozonoff, & Cohen, 2006; Martyr & Clare, 2012). Research indicating that AD pathophysiology begins years, and possibly even decades, before the onset of clinical symptoms has spurred the exploration of preclinical markers of future cognitive decline (Sperling et al., 2011). However, only very limited work has been conducted to assess EF abilities in individuals at this early, preclinical stage. One promising recent finding suggested that EF was sensitive to subtle differences between cognitively intact elders who differ by family history (FH) of AD when power was increased by examining multiple tests collectively (e.g., verbal fluency, Trail-making and Stroop; Donix et al., 2012).

One classic and robust test of EF is the Wisconsin Card Sorting Test (WCST). Examinees are asked to individually match test cards to one of four possible key cards depicting various shapes and colors (Grant & Berg, 1948; Heaton, 1981; Heaton, Chelune, Talley, Kay, & Curtis, 1993). The correct sorting principle is never explicitly stated and is changed without warning several times during the test after the participant makes multiple consecutively correct matches (i.e., after each category is achieved). The examinee is expected to use experimenter feedback (i.e., correct or incorrect) to deduce the sorting principle and to shift strategy to learn each new rule.

When it was first introduced as a neuropsychological testing instrument, use of the WCST focused primarily on the assessment of frontal lobe lesions, which resulted in poor EF test performance (Miyake et al., 2000). Specifically, frontal lobe lesions are linked to decreased response inhibition and subsequent difficulty shifting to a new sorting principle on the WCST, a concept that has been termed perseveration (Eling, Derckx, & Maes, 2008). In addition to perseveration, the WCST measures abstract reasoning by tapping into the ability to deduce the correct matching principles throughout the test (despite the lack of concrete instructions), as well as the ability to shift cognitive strategies when the matching principle suddenly changes (Heaton et al., 1993). More important, as understanding of the construct of EF has improved, the WCST has become much more broadly used to evaluate EF and frontal lobe functioning in healthy brains and in various disorders, including AD (Eling et al., 2008).

Evidence suggests that the WCST is sensitive to AD, differentiating individuals with AD from healthy controls, discriminating between AD groups based on disease severity, and distinguishing AD from other types of dementia. Specifically, greater perseveration is apparent in those with AD and mild cognitive impairment (often viewed as prodromal AD) than in healthy controls (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993; Nagahama et al., 2003); and those at later, more severe stages of AD achieve fewer WCST categories than those at milder stages of the disease (Bondi et al., 1993). Finally, the number of Categories achieved, Unique Errors, and Total Errors can differentiate individuals with AD, vascular dementia, and healthy controls from each other (Chao, Hao, Chao, Shi, & Chao, 2013). Notably, these studies have typically used a modified WCST (Nelson, 1976) that is shorter and less complex than the traditional test, such as including only test cards that can be matched based on one sorting principle (e.g., Nagahama et al., 2003; Nelson, 1976; Takeda et al., 2010). This approach is often used because the degree of impairment in these populations otherwise leads to frequent inability or refusal to complete the test.

Given the sensitivity of at least the simplified versions of the WCST to AD, examining performance among cognitively intact individuals who are *at risk* for AD could provide valuable insight into preclinical cognitive changes and potential markers for future cognitive

decline. Second only to advancing age, having a relative with AD (particularly a first-degree relative such as one or both parents) is the most significant risk factor for developing AD (e.g., Mosconi et al., 2010; Silverman et al., 1994). A number of cognitive and neural differences between cognitively intact individuals with a FH of AD and those without such history have been described (cf. Mosconi et al., 2010), which strongly suggests a genetic basis as at least a prominent route of transmission of AD. Although studies assessing FH alone cannot speak to the specific underlying genetic mechanisms, FH is a cost-effective and noninvasive method to assess risk for AD that can examine potential early markers for AD in intact elders, possibly including EF. It is currently unknown whether the WCST, either modified or traditional form, would be sensitive to early or subtle effects of AD risk on executive functioning. Given a cognitively intact sample, it was deemed most appropriate to retain the complexity of the traditional WCST toward capturing early, subtle differences in performance that might be revealed by FH. To this end, the present study examined performances on the traditional WCST in cognitively intact older adults with a FH of AD and compared them with the performances of comparable elders with no AD FH. We predicted that a positive FH of AD would be associated with poorer performance.

Method

Participants and Procedure

Forty-two older adults participated in the present study (see Table 1). All protocols were approved by the local Institutional Review Board and participants received compensation. They were recruited from the local community via newspaper advertisements that highlighted recruiting healthy participants with a family member diagnosed with AD. Family history was defined by presence (FH^+) or absence (FH^-) of a first degree relative (i.e., parent or sibling) with diagnosed AD; autopsy confirmation of diagnosis was not required. Eighteen participants had first degree FH of AD: 2 with both maternal and paternal, 9 maternal only, 5 paternal only, and 2 by siblings (1 with a twin sister, and 1 with both a brother and a sister). The FH survey was collected during the first session but not tabulated by the examiner until after testing was concluded; thus, it was not a

determinant for or a condition of study inclusion and FH status was not explicitly known by the examiner during testing. All participants were in good general health with few reports of chronic, acute, or past health conditions or smoking ($n = 3$) and no reports of substance abuse. The only notable chronic condition was high blood pressure: 48% of the sample ($n = 20$) reported being treated for blood pressure control (54% of FH⁻; 39% of FH⁺). No health conditions varied significantly in frequency between FH groups (all χ^2, $p > .35$).

Table 1

Descriptive Statistics (Mean (SD)) for Demographic and Screening Tests by AD Family History Group

	All	FH⁻	FH⁺	Between-groups p
n	42	24	18	
Age (years)	67.89 (9.79)	69.23 (10.67)	66.11 (8.42)	0.31
Education (years)	15.25 (2.43)	14.88 (1.94)	15.75 (2.94)	0.25
Sex	Female = 28	Female = 18	Female = 10	0.21[a]
	Male = 14	Male = 6	Male = 8	
MMSE	28.93 (1.22)	28.75 (1.39)	29.17 (0.92)	0.28
SKT	33.81 (3.80)	34.35 (2.74)	33.11 (4.83)	0.34
BDI	4.67 (4.16)	5.29 (4.63)	3.83 (3.38)	0.27
BAI	2.36 (2.52)	2.83 (2.88)	1.72 (1.81)	0.16

Note. FH = family history of AD; MMSE = Mini Mental State Exam raw score (out of 30); SKT = Synonym Knowledge Test raw score (out of 40); BDI = Beck Depression Inventory-II raw score (0–63 possible, all participants 0–19, median = 3.00); BAI = Beck Anxiety Inventory raw score (0–63 possible, all participants 0–12, median = 2.00).
[a] χ^2 test (all others based on independent t tests).

Materials and Procedure

Informed consent was obtained from all participants at the start of the testing session. Participants then completed several neuropsychological tests and surveys, only a subset of which was examined for the present study.

Mini-Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, & McHugh, 1975) was administered to screen for global cognitive functioning. This measure provides indices of orientation to time and place, word registration, attention and calculation, word recall, naming, repetition, comprehension, reading, writing, and drawing. All participants were

required to score at least 24 out of 30 to be included in the larger study from which these data were taken; this criterion is consistent with classic cutoffs for intact cognitive performance (Tombaugh & McIntyre, 1992). Recent research has also emphasized the use of 27 as a cut-off score to improve sensitivity and specificity in highly educated White examinees (e.g., O'Bryant et al., 2008), which also characterizes our sample. Only four participants in the present study scored below 27. Each of these four scored 26, which was due principally to poor performance on the Serial 7s Attention item (4 points lost on Serial 7s, $n = 2$; 3 points lost on Serial 7s, $n = 1$; and 2 points lost on Serial 7s, $n = 1$).

Synonym Knowledge Test (SKT)

The SKT is a computerized version of the Shipley Institute of Living Scale Vocabulary subtest (Langenecker, Zubieta, Young, Akil, & Nielson, 2007; Shipley, 1946), which was administered to estimate verbal intelligence. On each of 40 trials, participants indicated via keyboard press which word out of the four answer options best matched the meaning of a target word presented at the top of the screen. One participant in the FH⁻ group did not complete this test because of technical difficulties.

Beck Depression Inventory-II (BDI-II)

The BDI-II (Beck, Steer, & Brown, 1996) is a 21-item self-report instrument assessing depressive symptoms. Participants in the present study had scores within the minimal range (0–13 = minimal) except one FH⁻ participant who fell in the mild range at 19 (14–19 = mild).

Beck Anxiety Inventory (BAI)

The BAI (Beck & Steer, 1993) is a 21-item self-report instrument assessing common symptoms of anxiety. Participants in the present study had scores between 0 and 7, which were within the minimal range (0–7 = minimal) except one FH⁻ participant who fell in the mild range at 12 (8–15 = mild).

Wisconsin Card Sorting Test (WCST)

The WCST (Grant & Berg, 1948; Heaton, 1981; Heaton et al., 1993) is classic test of executive functioning. Participants were provided two decks of cards and asked to match each card, one at a time, to one of four key cards, after which they received feedback from the experimenter (i.e., correct or incorrect). Test cards can be matched to the key cards based on "color" (red, green, blue, or yellow), "form" (triangle, star, cross, or circle), and/or "number" (1, 2, 3, or 4 shapes on the card), with some cards matching the key cards based on multiple sorting principles (i.e., a test card depicting two green circles would match a key card depicting two green triangles based on both the number and color principles). However, only one of these sorting principles is correct at any given time and the correct sorting principle changes each time the participant achieves 10 consecutive correct responses (i.e., one completed category). The correct sorting principle is initially unknown to the participant and is never explicitly stated by the examiner during the test. The participant is told that the experimenter cannot tell him or her *how* to match the cards, but will indicate after each trial whether the participant's card placement was correct or incorrect. Participants are expected to utilize this feedback to learn the correct sorting principle to accurately advance through the test.

Herein, participants matched each of the cards until they had correctly completed six categories or placed all 128 cards, whichever came first. The following metrics were examined in the present study: Categories Achieved (number of sets of 10 consecutive correct responses completed out of six possible), Trials to Complete First Category (number of trials completed before obtaining the first set of 10 consecutive correct responses), Failure to Maintain Set (number of times the set was lost after five or more consecutive correct responses), Percent Conceptual Level Responses (percent of all completed trials in which there were three or more consecutive correct responses), Total Errors (total number of incorrect trials), Perseverative Errors (total number of errors involving preservation to the previously established sorting principle), and Non-Perseverative Errors (total number of errors that did not involve preservation).

Results

Table 1 presents the demographic and descriptive statistics on the sample. There were no significant differences between the FH⁻ and FH⁺ groups based on age, sex, or years of education. Furthermore, these groups did not differ significantly on screening tests of depression (BDI-II) or anxiety (BAI). Only four participants in the sample reported taking antidepressant medications; three in the FH⁻ group, one in the FH⁺ group. The groups were also comparable in global cognitive functioning (MMSE) and vocabulary (SKT). All participants scored within normal limits on the MMSE (16 participants [8 in each FH group] = score of 30; 16 participants [10 FH⁻, 6 FH⁺] = 29; 5 participants [2 FH⁻, 3 FH⁺] = 28; 1 participant [FH⁺] = 27; 4 participants [all FH⁻] = 26). Scores on the SKT were above average for the general population, as would be expected in this age and educational range (cf., Creed & Wiener, 1999).

To examine whether any demographic variables contributed to performance on the WCST, exploratory correlations were performed between the demographic variables, basic cognitive functioning indices, and the WSCT performance variables. These are presented in Table 2. Education did not differ between groups and was not correlated with any study variables except Failure to Maintain Set, only in the FH⁺ group. However, age and sex were correlated with the WCST in multiple comparisons. Specifically, greater age was associated with poorer performance in the overall sample, which was driven by significant correlations with several test metrics specifically in the FH⁺ group. Sex was significantly correlated with some of the same metrics, but only in the FH⁻ group, such that being male was associated with poorer performance. General cognitive functioning (MMSE, SKT) did not significantly correlate with WCST indices except in the FH⁻ group, where a greater number of Categories Achieved was associated with higher SKT performance.

Table 2
Correlations Amongst Study Variables

	Sex	Edu	MMSE	SKT	WCST-CA	WCST-TCFC	WCST-FMS	WCST-PCLR	WCST-TE	WCST-PE	WCST-NPE
Age											
All	−.02	.20	−.32*	−.25	−.27	.22	−.04	−.32*	.35*	.39**	.16
FH⁻	−.10	.29	−.37	−.51*	−.18	.02	−.08	−.21	.23	.27	.17
FH⁺	.00	.19	−.12	−.10	−.66**	.51*	.07	−.74**	.77**	.79**	.34
Sex											
All	—	−.10	−.21	.25	.16	−.31*	−.11	.19	−.18	−.16	−.15
FH⁻	—	−.04	−.25	.15	.51*	−.36	−.25	.48*	−.44*	−.51*	−.32
FH⁺	—	−.08	−.08	.28	−.08	−.27	−.11	−.11	.12	.10	.11
Edu											
All		—	.23	.18	.05	−.07	−.22	.05	−.03	.06	−.18
FH⁻		—	.12	.29	.26	−.36	−.14	.21	−.25	−.23	−.20
FH⁺		—	.36	.20	.14	−.03	−.47*	.11	−.06	.07	−.30
MMSE											
All			—	.15	−.06	.05	.00	.00	.00	.07	−.13
FH⁻			—	.20	−.05	.05	.16	.11	−.11	−.09	−.13
FH⁺			—	.22	.08	−.02	−.40	.10	−.07	.09	−.37
SKT											
All				—	.08	−.13	−.24	.12	−.15	−.12	−.17
FH⁻				—	.42*	−.24	.06	.35	−.35	−.38	−.30
FH⁺				—	−.09	−.05	−.43	−.06	.02	.03	−.03

Note. FH = family history of AD; Edu = years of education; MMSE = Mini Mental State Exam; SKT = Synonym Knowledge Test; WCST = Wisconsin Card Sorting Test; CA = Categories Achieved; TCFC = Trials to Complete First Category; FMS = Failure to Maintain Set; PCLR = Percent Conceptual Level Responses; TE = Total Errors; PE = Perseverative Errors; NPE = Non-Perseverative Errors.
* $p < .05$. ** $p < .01$.

FH group differences on the WCST measures were analyzed first using multivariate analysis of variance (MANOVA), using age and sex as covariates because of the observed correlations. The overall model was not significant for either covariate (age $p = .16$, sex $p = .19$) but was significant for FH ($F(8, 31) = 2.52$, $p = .03$, $\eta_p^2 = .39$, Wilks' λ = 0.61). Univariate ANOVA was then performed for each measure. These results are depicted in Figure 1. There were no significant covariate effects of sex, but significant covariance with age was found for Total Errors, Perseverative Errors, Percent Conceptual Level Responses, and Categories Achieved (ps < .01). After including these covariates in the model, significant group differences emerged for multiple indices: Categories Achieved, $F(1, 38) = 15.08$, $p < .001$, $\eta_p^2 = .28$; Percent Conceptual Level Responses, $F(1, 38) = 13.27$, $p = .001$, $\eta_p^2 = .26$; Total Errors, $F(1, 38) = 12.26$, $p = .001$, $\eta_p^2 = .24$; Perseverative Errors, $F(1, 38) = 10.94$, $p = .002$, $\eta_p^2 = .22$; and Non-Perseverative Errors, $F(1, 38) = 5.90$, $p = .02$, $\eta_p^2 = .13$. Specifically, those in the FH⁺ group achieved significantly fewer categories, exhibited a significantly lower percentage of Conceptual Level Responses, and committed significantly more errors than those in the FH⁻ group. No significant differences between groups emerged for Trials to Complete First Category, $F(1, 38) = 1.63$, $p = .21$, $\eta_p^2 = .04$, or Failure to Maintain Set, $F(1, 38) = 0.51$, $p = .48$, $\eta_p^2 = .01$.
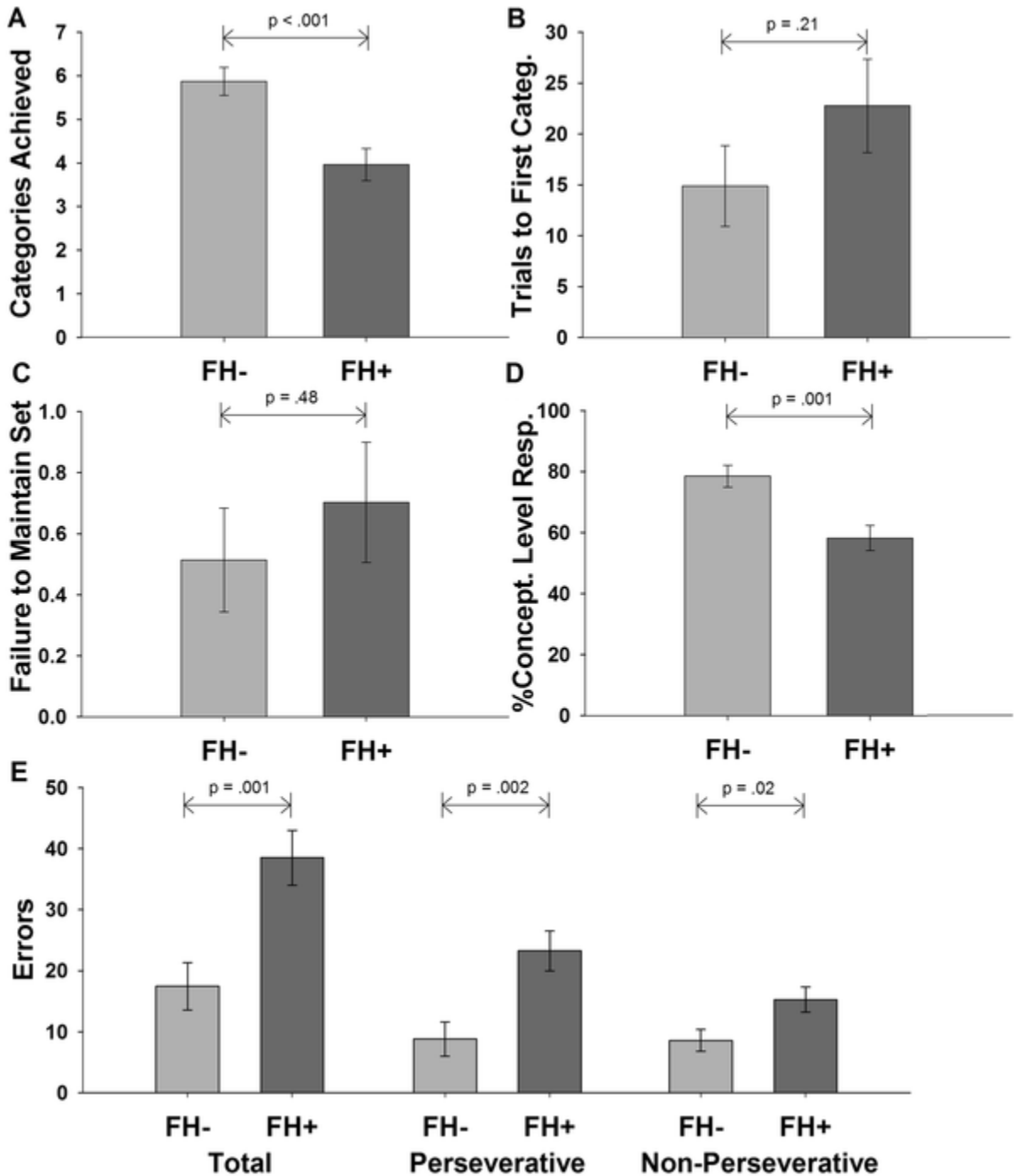
Figure 1. *Cognitively intact older adults with a positive family history of AD achieved significantly fewer categories, obtained a lower percentage of conceptual level responses, and committed more errors (total, perseverative, and non-perseverative) than those with no family history of AD.*

To further explore the degree to which FH predicts performance on the WCST, hierarchical regression analyses were conducted based on the five WCST performance variables for which significant differences emerged between FH risk groups (i.e., Categories Achieved, Percent Conceptual Level Responses, Total Errors, Perseverative Errors, and Non-Perseverative Errors). In each model, age, sex, and education were entered in Step 1 and FH was added in Step 2. Demographic variables were included in the model because of the significant exploratory correlations with WCST subscores, as well as because previous literature suggests that these variables may play a role in WCST performance (Boone, Ghaffarian, Lesser, Hill-Gutierrez, & Berman, 1993; Heaton, 1981; Heaton et al., 1993). Given the small sample size and lack of significant correlations for the MMSE and the SKT with the WCST, they were not included in the regressions to help reduce over-fitting the models. Depression and anxiety scores were similarly excluded to prevent over-fitting and because of the extreme score restriction; little depression or anxiety was reported in the sample (see Table 1).

Results of the hierarchical regression analyses are presented in Table 3. For each of the five regression analyses, the models failed to reach significance based solely on the demographic variables entered in Step 1. However, when FH was entered in Step 2, all five of the models reached significance. Moreover, although the statistics shown in Table 3 depict a significant contribution of age as a predictor of WCST performance in all models (as well as education, to a modest degree), it is evident that FH added significantly to each of these predictions, above and beyond the contribution of age alone. Indeed, FH accounted for more variance in each model than the other three variables combined.

Table 3
Hierarchical Regression Analyses Predicting Performance on the WCST

	Model summary of each step				Contribution of each variable in last step				
	R^2	ΔR^2	F	p	B	SE	β	t	p
Categories Achieved									
Step 1	.11	—	1.57	.21					
Age					−0.08	0.03	−0.41	−3.08	.004
Sex					0.21	0.50	0.06	0.42	.68
Edu					0.18	0.10	0.24	1.80	.08
Step 2	.41	.29	6.29	.001					
FH					−2.09	0.49	−0.57	−4.28	<.001
% Conceptual Level Responses									
Step 1	.15	—	2.29	.09					
Age					−0.96	0.28	−0.46	−3.46	.001
Sex					3.91	5.62	0.09	0.80	.49
Edu					2.06	1.13	0.24	1.82	.08
Step 2	.41	.26	6.51	<.001					
FH					−22.38	5.53	−0.54	−4.05	<.001
Total Errors									
Step 1	.16	—	2.46	.08					
Age					1.08	0.30	0.47	3.57	.001
Sex					−3.79	6.12	−0.08	−0.62	.54
Edu					−2.02	1.23	−0.22	−1.65	.11
Step 2	.40	.24	6.20	.001					
FH					23.11	6.02	0.52	3.84	<.001
Perseverative Errors									
Step 1	.17	—	2.72	.06					
Age					0.81	0.23	0.49	3.61	.001
Sex					−2.20	4.54	−0.07	−0.48	.63
Edu					−0.83	0.91	−0.12	−0.92	.37
Step 2	.37	.20	5.53	.001					
FH					15.28	4.47	0.47	3.42	.002
Non-perseverative Errors									
Step 1	.10	—	1.37	.27					
Age					0.27	0.14	0.29	1.99	.053
Sex					−1.50	2.73	−0.08	−0.55	.59
Edu					−1.19	0.55	−0.32	−2.18	.04
Step 2	.27	.17	3.39	.02					
FH					7.90	2.70	0.44	2.94	.006

Note. Edu = years of education; FH = family history of AD.

Discussion

In the present study, healthy, cognitively intact older adults with a family history of AD had significantly poorer scores on the WCST, a classic measure of executive functioning, than comparable elders without a family history of AD. Specifically, those with AD family history completed fewer categories, exhibited a lower percentage of conceptual level responses, and committed more errors. This was despite their normal scores on measures of general cognitive functioning, generally high level of education, and good health. Moreover, hierarchical regression analyses confirmed the role of AD family history in WCST performance. Although greater age predicted poorer performance for each metric, family history also significantly predicted performance. Indeed, the models failed to reach significance with demographic variables alone and family history contributed far more variance to the models. The results are consistent with studies showing that the WCST is sensitive to AD (e.g., Bondi et al., 1993;

Chao et al., 2013; Nagahama et al., 2003), and extended them to show its sensitivity to risk for AD in cognitively intact elders. The results also complement and extend a recent report showing the sensitivity of a battery of executive measures to FH in cognitively intact elders (Donix et al., 2012). In the present study, a single test was robustly sensitive to differences by FH.

The number of trials necessary to complete the first set was comparable between the groups. However, conceptual level responding was poorer in the FH$^+$ group. This is indicative of poor insight into the correct sorting strategy, which is necessary for accurate shifting of set when the sorting principle changes. The greater number of errors and fewer number of categories completed in the FH$^+$ group are also consistent with poorer insight into the sorting strategy. Increased perseveration in older adults has previously been linked to such set-shifting difficulties (Ridderinkhof, Span, & van der Molen, 2002). Additionally, evidence from the Stroop test, another commonly used EF measure, indicates set-shifting impairment among those with AD, because of difficulty suppressing previously relevant rules and learning new rules across multiple variations of the Stoop test (Amieva et al., 2004a). Similar, albeit less severe, difficulties were evident in the cognitively intact FH$^+$ participants in the current study.

Failures of maintaining set were also comparable between groups. Thus, once the set was achieved, it appears that both groups were able to maintain it. However, closer consideration of the WCST suggests an alternative explanation. Although FH$^-$ participants exhibited few set maintenance failures because of accurate category completion, FH$^+$ participants obtained too few consecutively correct responses (i.e., five or more are required) to meet the criteria for a "Failure to Maintain Set" when an error occurred. That is, one must accurately change set, maintain the new set for five or more trials, and subsequently lose set to commit a Failure. Thus, set-shifting difficulties in the FH$^+$ group prevented them from accurately changing set in the first place. Further confirmation of this is shown in their higher error rates and poorer conceptual level responding, rather than difficulty maintaining set.

Our findings, in conjunction with findings regarding the sensitivity of the WCST in detecting AD (Bondi et al., 1993; Chao et

al., 2013; Nagahama et al., 2003), speak to the importance of examining cognitive domains other than memory to better understand risk for and manifestation of AD. Executive functioning is one domain recognized by the National Institute on Aging and the Alzheimer's Association in their recent diagnostic recommendations, which include a classification for nonamnestic AD specifically characterized by executive dysfunction (McKhann et al., 2011). The executive abilities necessary for successful completion of the WCST (e.g., sustained attention, set shifting, inhibition, and planning) are similar to those required for daily functioning and WCST performance has been linked to the ability to complete activities of daily living (Jefferson et al., 2006; Martyr & Clare, 2012). Despite the empirical focus on memory deficits in AD, these executive processes are also affected by AD. Deficits in this domain are, in fact, among the first nonmemory impairments to emerge with AD onset (Amieva, Phillips, Della Sala, & Henry, 2004b). Moreover, these executive deficits may be related to, or even underlie, certain aspects of memory decline (Baudic et al., 2006; Gleichgerrcht et al., 2011; Hasher et al., 2007). Further research elucidating the role of EF in risk for AD is, therefore, necessary. As research within this domain progresses, however, it will be important to more fully examine the unique and shared contributions of these executive abilities and memory in determining risk for AD. Indeed, previous findings suggest co-occurring and age-related neural network changes underlying both EF and memory (Buckner, 2004). However, evidence also supports dissociation of these networks (Buckner, 2004). Future work assessing EF and memory in the same study, as well as their neural underpinnings, will be important for understanding the independent risk each domain confers to AD development. This may be particularly important and impactful at early stages of disease progression. The assessment of executive functioning in those at risk for AD, but at a stage before clinically acknowledged disease onset, is imperative for broadening the current literature and the clinical utility of such commonly used executive functioning measures.

Given the importance of assessing risk for AD early in the course of disease progression and ideally before disease onset, the examination of *cognitively intact* older adults was the focus of the present study. The most commonly used cutoff for the MMSE to define intact cognitive functioning is 24 (Lopez, Charter, Mostafavi, Nibut, &

Smith, 2005; Mitchell, 2009; Tombaugh & Mcintyre, 1992). However, the use of a cut-off score of 27 has recently been emphasized to improve sensitivity and specificity in highly educated White examinees (e.g., O'Bryant et al., 2008). The four participants in the present study who scored below 27 all obtained a score of 26, principally because of poor performance on the Serial 7s Attention item. This pattern of difficulty is consistent with previous research describing early decline with advancing age for this item (e.g., Ishizaki et al., 1998). Although the alternate item (*WORLD* backward) is considered easier (e.g., Ganguli et al., 1990) and is often administered and scored instead when poor performance results on Serial 7s (e.g., Crum, Anthony, Bassett, & Folstein, 1993), this procedure was not used in the present study. Thus, it is likely that all our participants would have achieved at least 27 had that procedure been used. Regardless, such attention to cutoff ranges on the MMSE is likely not very meaningful given the blunt nature of the instrument (cf. Lopez et al., 2005). Moreover, all four of the participants with scores of 26 were in the FH⁻ group (the better performers on the WCST), which alleviates concern about the contribution of poor general cognitive performance to the pattern of the present results. As confirmation of that conclusion, we removed these four participants from the analysis, but the pattern of results was unchanged.

This study was not without limitations. First, the study sample was rather small and thus it is unclear whether these findings would generalize to a larger, and potentially more diverse, group. However, very robust effects of AD family history on WCST performance were evident even in a sample of this size. Given the small group sizes, statistical analyses based on specific familial relationship of AD family history (e.g., parent vs. sibling, maternal vs. paternal) could not be conducted in the present study. However, the strong criteria for FH (i.e., first-degree relative required) and the high rate of FH originating from the maternal side, which tends to convey greater risk (e.g., Johnson et al., 2014; Reiter et al., 2012), may have helped to strengthen the findings. Second, family history was determined by participant report. Confirmation of diagnosis was not available through medical records or autopsy confirmation. Furthermore, although sex correlated with WCST performance in the FH⁻ group, the relatively small number of males in the sample precluded a thorough investigation of these relationships. Additional research with a larger,

more balanced sample would be helpful in clarifying the role of sex in WCST performance and evaluating whether it interacts with other predictors such as age and AD family history.

The differences in the present study attributable to family history risk for AD signal an inherited factor that affects executive functioning. Assessment of FH is extremely cost-effective and noninvasive, making it a very efficient method of assessing risk. Moreover, recent reports suggest that the cognitive and cortical differences associated with FH are separable from at least some known genetic risks for AD (e.g., La Rue et al., 2008; Reiter et al., 2012), signaling that FH may represent an as of yet unknown factor that can modulate the effects of such genes (e.g., Bendlin et al., 2010; Johnson et al., 2006; Xu et al., 2009). Nonetheless, the more precise basis of inherited risk cannot be discerned by family history assessment alone. Future investigation of the genetic and other lifestyle contributions (e.g., nutrition, socioeconomic status, etc.) to this effect would be important. Although there are multiple hereditary factors associated with AD, the apolipoprotein-E (APOE) ε4 allele is a well-recognized, important risk factor for AD that is also associated with familial clustering (e.g., Saunders et al., 1993a, 1993b). Furthermore, its presence has been associated with differential brain activity patterns, including in the frontal lobes, in studies with cognitively intact elders (e.g., Hantke et al., 2013; Seidenberg et al., 2013; Smith et al., 2014) and the literature as a whole supports a robust negative effect of APOE ε4 on multiple domains of cognition in healthy elders, including executive functioning (Wisdom, Callahan, & Hawkins, 2011).

The distribution of APOE ε4 allele in our sample is not known, but differential performance on the WCST could be because of APOE ε4 inheritance. One study supporting this idea (Wetter et al., 2005) showed that ε4 carriers differed from noncarriers on the DKEFS Color-Word Interference Test (Delis, Kaplan, & Kramer, 2001), a task similar to the Stroop (1935) test, specifically on an inhibition/switching condition that may tap skills comparable with those required by the WCST. In contrast, other studies found no general difference on the WCST in cognitively intact elders by ε4 (Caselli, Reiman, Hentz, Osborne, & Alexander, 2004; Etnier et al., 2007), although in one (Caselli et al., 2004) there were interactive effects where ε4 noncarriers with high trait anxiety outperformed high-anxiety ε4

homozygotes, carriers of the highest risk allele combination that occurs in only about 2% of the general population (e.g., Mahley, 1988; Saunders et al., 1993b); no differences existed for ε4 heterozygotes. Although the current study cannot directly address APOE ε4 or trait anxiety findings, it notably supports robust effects of AD family history on WCST performance in healthy elders, which is not yet matched by studies using APOE ε4 as the measure of risk. Moreover, recent studies report FH effects on cognitive (Donix et al., 2012; La Rue et al., 2008) and cortical changes with age (Reiter et al., 2012) that are distinct from APOE ε4 contributions, and some suggest that FH may modulate the effect of ε4, suggesting that a different factor underlying FH influences the expression of APOE ε4 on neural structure (Bendlin et al., 2010) and functioning (Johnson et al., 2006; Xu et al., 2009). Additionally, Donix and colleagues (2012) reported that although cognitively intact elders had poorer executive functioning than their lower risk counterparts, FH did not contribute to decline over time, whereas APOE ε4 did. The current study did not investigate change over time. Thus, there is yet need for much investigation into the effects of AD family history on cognitive aging separately from and in conjunction with known genetic risks such as APOE ε4. A longitudinal approach to such investigations would be particularly beneficial for identifying predictors of cognitive decline and disease progression. Our study suggests these investigations should specifically target executive functioning, likely using multiple executive tasks (including WCST) within the same sample, to elucidate the nuanced characteristics of the various aspects of EF that are and are not subject to early stage vulnerability to AD risk factors.

In conclusion, this study demonstrated that family history of AD was significantly associated with poorer executive functioning performance on the traditional WCST among cognitively intact elders. These findings expand the literature regarding executive functioning abilities as they relate to aging and risk for AD, highlighting the need to examine cognitive domains beyond memory. These results underscore the importance of considering executive abilities as part of the exploration of potential early markers of future cognitive decline.

Footnotes

[1] Note that education was not included as a covariate because of the sample size and its overall lack of correlation with the outcome variables. However, when included, it did not serve as a significant covariate in the overall model or for Failure to Maintain Set.

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