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A Diffusion Model Analysis of Episodic Recognition in Preclinical Individuals With a Family History for Alzheimer's Disease: The Adult Children Study

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Objective: A family history of Alzheimer's disease (AD) increases the risk of developing AD and can influence the accumulation of well-established AD biomarkers. There is some evidence that family history can influence episodic memory performance even in cognitively normal individuals. We attempted to replicate the effect of family history on episodic memory and used a specific computational model of binary decision making (the diffusion model) to understand precisely how family history influences cognition. Finally, we assessed the sensitivity of model parameters to family history controlling for standard neuropsychological test performance. ***Method:*** Across 2 experiments, cognitively healthy participants from the Adult Children Study completed an episodic recognition test consisting of high- and low-frequency words. The diffusion model was applied to decompose accuracy and reaction time (RT) into latent parameters which were analyzed as a function of family history. ***Results:*** In both experiments, individuals with a family history of AD exhibited lower recognition accuracy and this occurred in the absence of an apolipoprotein E (APOE) ε4 allele. The diffusion model revealed this difference was due to changes in the quality of information accumulation (the drift rate) and not differences in response caution or other model parameters. This difference remained after controlling for several standard neuropsychological tests. ***Conclusions:*** These results confirm that the presence of a family history of AD confers a subtle cognitive deficit in episodic memory as reflected by decreased drift rate that cannot be attributed to APOE. This measure may serve as a novel cognitive marker of preclinical AD.

Keywords: Alzheimer's disease, family history, memory, diffusion model

There is a growing body of evidence indicating that Alzheimer's disease (AD) pathology can accumulate decades before the onset of clinically detectable symptoms (Bateman et al., 2012; Price & Morris, 1999; Price et al., 2009). Therefore, it is critical to characterize this preclinical phase of the disease to understand an individual's risk of developing dementia and to monitor behavioral profiles that may be targets for treatments as they become available. For these reasons, substantial research effort has been devoted to identifying biological and cognitive markers that herald the onset of symptomatic AD.

One approach to characterizing preclinical AD is to examine the profile of biomarkers in individuals who have a genetic predisposition to developing the disease. The primary genetic risk factor for AD is the presence of the apolipoprotein E (APOE) ε4 allele (Saunders et al., 1993). Individuals who possess this allele exhibit abnormal biomarker levels compared with ε4 negative participants (Morris et al., 2010; Storandt, Head, Fagan, Holtzman, & Morris, 2012) and also show slight deficits on tests of executive functioning and episodic memory performance as shown by several meta-analyses (Small, Rosnick, Fratiglioni, & Backman, 2004; Wisdom, Callahan, & Hawkins, 2011). In addition to APOE, other genetic factors contributing to AD risk have been identified (Bertram et al., 2007; Hollingworth et al., 2011; Naj et al., 2011). Such factors can be examined by testing individuals who have a family history for AD. Indeed, having at least one first degree relative with AD substantially increases an individual's risk of also developing the disease (Donix, Small, & Bookheimer, 2012; Huang, Qiu, von

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Strauss, Winblad, & Fratiglioni, 2004; Jayadev et al., 2008; Martinez et al., 1998).

It is important to note that factors associated with family history (hereafter called the "family history effect") have been shown to affect many of the neurobiological indicators of AD pathology even in cognitively healthy individuals. These indicators include changes in hippocampal structure (Donix et al., 2010), gray matter volume (Honea, Swerdlow, Vidoni, Goodwin, & Burns, 2010), white matter integrity (Bendlin et al., 2010; Xiong et al., 2011), glucose metabolism (Mosconi et al., 2007), functional neural activation during cognitive tasks (Johnson et al., 2006; Xu et al., 2009), resting state functional connectivity (Wang et al., 2012), and amyloid burden (Mosconi et al., 2010; Xiong et al., 2011).

Despite the relatively widespread effects of family history on well-established biomarkers of AD, sensitive cognitive markers have been more difficult to identify above and beyond the presence of an APOE4 allele. When such effects are found, they tend to be particularly subtle. For example, in one comprehensive study, Xiong et al. (2011) examined the effect of family history on measures of attention, memory, language, and processing speed and generally found no differences with the exception of memory for consonant trigrams. However, an earlier age of parental onset of AD symptoms was correlated with greater global switch cost in a consonant-vowel/odd-even switching task and also with lower performance on the Similarities subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997). Similarly, La Rue et al. (2008) showed that family history was associated with subtle differences in serial recall curves such that individuals with a family history of AD tended to recall more recently presented words (i.e., exhibited a greater recency effect) compared with no history controls, despite having recalled an equal number of items overall. Other studies have found little evidence for family history effects on baseline assessments of standard neuropsychological measures (e.g., Donix et al., 2010; Hayden et al., 2009; Johnson et al., 2006; Mosconi et al., 2007; Okonkwo et al., 2012). It should be noted that one study has shown relatively widespread family history differences on composite measures of processing speed, memory and executive functioning after controlling for APOE genotype (Donix et al., 2012). However, this study included a relatively small number of participants (23 family history− and APOE−; 19 family history+ and APOE−) and hence needs replication and extension.

Although a positive family history overlaps highly with the presence of an APOE ε4 allele (Zintl, Schmitz, Hajak, & Klunemann, 2009), it is likely that the effect of family history is multifaceted and possibly indexes non-APOE genetic factors, such as cerebrovascular disease or diabetes, or even nongenetic risk factors, such as socioeconomic status, family size, education, or cognitive reserve (Borenstein, Copenhaver, & Mortimer, 2006; Jarvik et al., 2008). Thus, it is important to determine whether family history confers additional cognitive risk that is independent of that due to APOE. Relatively few studies have examined the joint influence of family history and APOE genotype on cognitive outcomes, but those that do have generally found no interaction between family history and APOE (Donix et al., 2012; Hayden et al., 2009; La Rue et al., 2008) suggesting that family history presents an independent cognitive risk factor that is not captured by APOE. However, another study did find evidence for an interaction on an episodic memory measure (Debette et al., 2009), such that the influence of family history was particularly magnified in APOE carriers compared with noncarriers. A similar pattern was found by Bendlin et al. (2010); however, no formal test of the interaction was performed. Thus, it is important to carefully delineate the cognitive deficits conferred by family history in otherwise healthy individuals to identify cognitive systems that are vulnerable to early pathology and use measures of those systems as a diagnostic tool and a marker of the effectiveness of interventions.

Although the exact nature of how family history and APOE interact to influence cognition has not been firmly established, according to recent estimates, 60% of individuals who develop sporadic AD do not carry an APOE4 allele (http://www.nia.nih.gov/sites/default/files/alzheimers_disease_genetics_fact_sheet_0.pdf). Thus, it is critical to isolate the cognitive effect of the risk factors that are indexed by family history, that are independent of the contaminating, albeit subtle, influence of APOE (e.g., Wisdom et al., 2011). Therefore, in the present study, we have chosen to examine individuals who do not carry the APOE4 allele to isolate the unique influence of family history on cognitive measures.

Although accuracy measures have shown sensitivity to AD pathology (Aschenbrenner et al., 2015; Duchek et al., 2013; Rodrigue et al., 2012; Sperling et al., 2013), such performance variables capture only the final outcome of a cascade of cognitive processes and hence do not characterize the underlying processes that occur before a response is executed. Measures of reaction time (RT) can provide additional insight into the ongoing process that ultimately leads to a correct or incorrect behavioral response. For example, aspects of the RT distribution are particularly sensitive to early-stage AD (Duchek et al., 2009, 2013; Tse, Balota, Yap, Duchek, & McCabe, 2010) and they can predict later conversion to symptomatic AD above and beyond standard neuropsychological tests (Balota et al., 2010). Specifically, RT distributions are positively skewed and measures relating to the variability of the slowest RTs show the most robust changes due to preclinical AD, at least in standard measures of attentional control. Possibly, a measure that combines all aspects of performance, including accuracy and the shape of the RT distribution, will be particularly sensitive to preclinical AD risk as indexed by family history.

Sequential sampling models combine accuracy and RT information from binary decision tasks. The most well-known instantiation of such models is Ratcliff's (1978) diffusion model. The diffusion model captures the proportion correct as well as the shape of RT distributions for correct and erroneous responses using four primary latent parameters (see Figure 1). As shown, the model assumes the noisy accumulation of evidence toward a given response boundary. In the context of an episodic recognition task for example, the boundaries would correspond to "old" and "new"

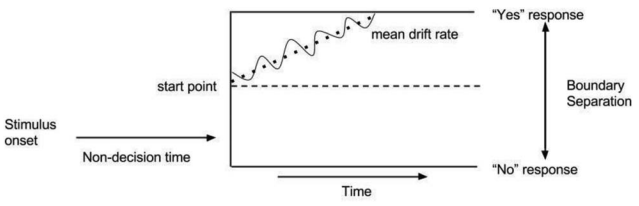

Figure 1. Major parameters of the Ratcliff diffusion model.

responses. The average rate of evidence accumulation is the drift rate and this reflects the quality of evidence that is extracted from the stimulus and accumulated across time. A higher drift rate will result in better accuracy as well as in faster and less variable RTs. Another primary parameter of the model is the boundary separation, which reflects response caution or the amount of evidence an individual requires before outputting a response. Wider boundaries correspond with slower RTs and higher accuracy. Other parameters include the starting point, which indicates bias toward one response over the other, and nondecision time, which captures peripheral processes such as motor execution. The fit of the model to experimental data can be improved by allowing for across trial variability in these parameters. For example, the drift may not be exactly identical across trials due to various factors such as fluctuations in attention over time. Thus, drift rate is assumed to be normally distributed with a variability parameter (η) and both start point and nondecision time are drawn from a uniform distribution with a width of s_z and s_{t0}, respectively.

A key benefit of the diffusion model is its ability to provide insight into underlying cognitive processes that cannot be identified from accuracy or RT data alone. The psychological interpretability of these latent parameters has been well established (Voss, Rothermund, & Voss, 2004). For example, when accuracy is emphasized in the task instructions, boundaries are correspondingly set to be wider (i.e., participants are more cautious), precisely as one would expect. Furthermore, the drift rate parameter has been strongly linked to individual difference measures including IQ (Ratcliff, Thapar, & McKoon, 2010) and working memory capacity (Schmiedek, Oberauer, Wilhelm, Süβ, & Wittmann, 2007), suggesting this parameter might index general cognitive control mechanisms. In addition, the drift rate is strongly related to the slow tail of the RT distribution, which has been shown to be particularly sensitive to early-stage AD in previous studies (Duchek et al., 2013; Tse et al., 2010). It is important to note that the diffusion model can provide insight into group differences on cognitive tasks without the confounding effects of differences in scale or overall response speed (Faust, Balota, Spieler, & Ferraro, 1999).

The relationship among the model parameters makes it clear that an examination of simple mean RTs or accuracy measures alone only provides the first step in understanding the underlying cognitive mechanisms. Indeed, a number of different configurations of model parameters could result in virtually identical performance at the level of either mean RT or overall accuracy (Voss, Nagler, & Lerche, 2013). Furthermore, there is the potential for group effects to manifest in "opposite" directions on different parameters and, thus, cancel differences in mean performance. For example, the deleterious effects of family history might manifest as a decreased drift rate (increasing RTs and lowering accuracy), but given that individuals are aware of their family history status they may become more cautious and increase their boundary separation (increasing both RTs and accuracy). Such a pattern would diminish the power to detect group differences when only accuracy is examined. This is precisely why it is important to have a processing model for a given task, which the diffusion model provides.

The diffusion model has already been applied to examine the influence of healthy aging on a number of basic tasks including brightness discrimination, lexical decision and episodic recognition (Ratcliff, Thapar, & McKoon, 2004, 2010, 2011; Spaniol, Madden, & Voss, 2006). The general pattern from these studies suggests that aging primarily influences boundary separation and nondecision time but not the drift rate. Critically, White, Ratcliff, Vasey, and McKoon (2010) demonstrated that the drift rate parameter was more sensitive to group differences due to clinical disorders than either accuracy or RT alone. This supports the use of the diffusion model as an early detection tool in clinical settings. No study has yet explored the utility of the diffusion model in discriminating individuals at varying risk for developing AD.

The relative sensitivity of diffusion model parameters to preclinical AD processes will likely depend on the particular task that is administered and we focus here on episodic recognition performance for two reasons. First, deficits in episodic memory performance are often considered the hallmark cognitive characteristic of AD (Albert, Moss, Tanzi, & Jones, 2001; Bäckman, Small, & Fratiglioni, 2001; Hodges, 2000), which is not surprising given that episodic retrieval depends on brain regions that are particularly vulnerable to the AD pathologic processes (e.g., Braak & Braak, 1991; Buckner et al., 2005). Second, as already mentioned, the diffusion model has been applied to recognition performance in healthy older adults and therefore we already have a good understanding of how model parameters should change with normal aging in this task. Specifically, Ratcliff et al. (2004) presented younger and older adults with high- and low-frequency items and found that (a) boundary separation and nondecision time increased with age, (b) drift rates tended to be higher for low-frequency words and nonstudied items, and (c) drift rates did not change significantly with age.

With this in mind, there were two primary goals of the present study. First, because the effects of family history on cognition have been sporadic in the literature, we were first interested in examining a relatively demanding episodic recognition test in demonstrating sensitivity to family history in cognitively healthy controls, without the potential confounding influence of an APOE4 allele, especially because the relative frequency of ε4 positive but family history negative individuals is relatively rare. Second, we evaluated the utility of applying the diffusion model to episodic recognition performance in characterizing the specific cognitive mechanisms that are affected in preclinical AD as defined by family history. Given its relationship to accuracy and the shape of the RT distribution, we expected the drift rate parameter of the diffusion model would show the most robust differences due to family history. However, it is possible that group differences may emerge for other model parameters as well, particularly the boundary separation. Although not of primary interest, we examined the sensitivity of the diffusion model parameters to family history after controlling for general neuropsychological test performance. These analyses will provide a greater understanding of the cognitive mechanisms that are changing in preclinical AD within a well-defined model of episodic recognition performance.

In pursuit of these goals, participants studied a list of high- and low-frequency words and were given a yes/no recognition test. Low-frequency words have been shown to produce higher recognition performance than higher frequency words (Glanzer & Adams, 1985). We chose to manipulate word frequency because of its known effect on the drift rate (Ratcliff et al., 2004) to insure we replicate these effects with the diffusion parameters, and because there is some evidence that very mild AD individuals have lower hit rates particularly for low-frequency words (Balota, Burgess,

Cortese, & Adams, 2002). Hence, it is possible that low-frequency words would be differentially sensitive to family history effects.

Experiment 1

Method

Participants. A total of 80 individuals with known family history were recruited through the Charles F. and Joanne Knight Alzheimer's disease Research Center as part of the Adult Children Study (ACS). This cohort represents a group of predominantly cognitively healthy adults who are stratified based on presence of a family history for AD. A positive family history (family history+) was defined as having at least one biological parent who developed symptomatic AD prior to 80 years of age whereas a negative family history (family history−) was defined as having both parents live to age 70 with no symptoms of AD. If an individual's parents showed signs of AD after age 70, his or her status was subsequently changed to family history positive. Parental AD was verified either by the parent being examined as part of other ongoing longitudinal studies on AD at Washington University or by examination of medical records.

All participants were screened for dementia by highly trained physicians using the Clinical Dementia Rating Scale (CDR: Morris, 1993). We were interested in cognitively healthy individuals and, thus, only participants who were given a CDR score of 0 indicating no symptoms of AD were included in the present study. The CDR is based largely on informant report of intraindividual change in ability to carry out daily activities. This informant based approach has been demonstrated to be highly sensitive in discriminating nondemented individuals from even the earliest symptomatic stage of AD (Carr, Gray, Baty, & Morris, 2000; Galvin et al., 2005). The diagnostic acumen of clinicians using the CDR has been well-validated by the presence of AD neuropathology at autopsy in 93% of the cases, including those in the earliest CDR 0.5 stage (Berg et al., 1998).

A comprehensive battery of neuropsychological tests was also administered by an examiner who was blind to the participant's CDR rating. Depending on the age of the participant at entry into the study, one of two neuropsychological test batteries was administered and tests that were administered in common included the Mini Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975), a test of working memory using the Letter Number Sequencing subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997), an episodic memory test using the Selective Reminding Test (Grober, Buschke, Crystal, Bang, & Dresner, 1988), a test of semantic retrieval using Animals Naming (Goodglass & Kaplan, 1983), and a test of visual-perceptual motor performance using Trail Making A (Armitage, 1946). Tests of associate learning and delayed recall were also administered but the particular test varied slightly across batteries. For associate learning, participants were given either the associate learning subtest of the Wechsler Memory Scale (Wechsler & Stone, 1973) or the Verbal Paired Associates test of the Wechsler Memory Scale—III (Wechsler, 1997). For the delayed recall test, either the Logical Memory Delayed recall from the Wechsler Memory Scale—Revised (Wechsler, 1987) or Logical Memory Delayed recall from the Wechsler Memory Scale—III (Wechsler, 1997) was used. The raw scores on each of the versions of the two tasks were standardized to allow for comparison across the batteries. It is important to note that these tests have previously been shown to discriminate healthy controls from mild and very mild dementia (Morris et al., 1991; Storandt & Hill, 1989). A measure of executive function using Trail Making B (Armitage, 1946) was also available and standardized across batteries in the same manner as the memory tests.

The demographic variables and neuropsychological test scores on these participants are presented in the left panel of Table 1. As can be seen, the groups are quite similar and no reliable group differences emerged on any of the measures. It is important to note that the MMSE scores were very high (mean >29) which coupled

Table 1
Demographics of Participants for Experiment 1 and Experiment 2

	Experiment 1				Experiment 2			
	Family history				Family history			
	Negative (N = 47)		Positive (N = 33)		Negative (N = 44)		Positive (N = 39)	
Variable/test	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	66	6.6	64	8.5	65	8.4	64	7.6
Education	16.4	2.6	16.3	2.4	15.9	2.7	15.7	2.4
MMSE	29.3	1.1	29.2	1.1	29.2	1.0	29.6	1.8
Animal Naming	24	6.2	22	5.1	23	6.1	22	4.9
Trails A	29	8.9	28	6.1	27	9.2	28	7.5
Trails B	0.14	0.78	0.10	0.85	0.11	0.85	−.10	0.89
Letter Number	12	2.6	12	3.2	11	2.9	11	3.1
Selective Reminding	33	6.2	31	5.6	33	6.0	33	6.5
Associate Learning	0.38	0.95	0.28	0.91	0.34	0.97	0.22	0.94
Logical Memory Delayed	0.11	0.86	−0.5	0.73	0.30	0.78	−.04	0.81

Note. The range of possible scores for each test is as follows: Animal Naming = 0 and above; Trail Making A = 0–180 s; Letter Number Sequencing = 0–21; Selective Reminding = 0–48. For all tests, a higher score indicates better performance with the exception of Trail Making A, for which a higher score indicates worse performance. The associate learning, logical memory delayed, and Trail Making B scores are z scored composites formed from two versions of each task. The tasks were standardized to the mean and standard deviation of cohort's first time completing each task. Higher scores indicate better performance. MMSE = Mini Mental State Examination.

with the statistically equivalent performance on the neuropsychological battery as well as the CDR 0 rating indicates these groups were cognitively healthy.

APOE genotyping. APOE genotyping was performed using Taqman assays (Applied Biosystems, Foster City, CA) for both rs429358 (ABI#C_3084793_20) and rs7412 (ABI#C_904973_10). Because the present study focuses on family history, independent of APOE4 allele, all participants were negative for the ε4 allele (ε22 = 1, ε23 = 14, ε33 = 65).

Recognition task. A total of 192 items were selected for the recognition task. We used the HAL frequency (Balota et al., 2007; Lund & Burgess, 1996) norms to designate 96 items as high frequency (mean log HAL = 10.4), and 96 as low-frequency (mean log HAL = 6.5). High- and low-frequency words were matched with respect to overall word length. The items were then split into two lists, study items and lure items, with equal numbers of high- and low-frequency items represented in each list. Participants were instructed that they would see a series of words appear on the computer screen one at a time. They were asked to remember each item for a later memory test. The order of presentation of the items was randomly determined for each participant. During each study trial, the target word appeared in the center of the screen and participants read the stimulus aloud into a microphone. After detecting a voice onset, the computer initiated a 2-s stimulus duration after which the next item was immediately presented.

After all study items were presented, the test phase began immediately. Participants were instructed that words would again appear, one at a time, in the center of the screen. They were to determine if the item was "old" (i.e., presented on the study list) or "new" (not presented on the study list) as quickly and as accurately as possible. Old items were indicated by pressing the P key on the computer keyboard and new items with the Q key. After each response, the item was removed from the screen and a 1,250-ms interval was initiated before the presentation of the next item. Participants were not given feedback regarding performance and order of presentation of items was randomly determined for each individual.

Statistical analysis. We quantified recognition accuracy by calculating signal detection for high- and low-frequency items. Group differences in accuracy were analyzed using a 2 (family history) × 2 (word frequency) mixed-effects analysis of variance (ANOVA) and differences in RT with a 2 (family history) × 2 (word frequency) × 2 (type: old or new items) mixed-effects ANOVA. Diffusion model parameters were analyzed using either a 2 (family history) × 2 (frequency) ×2 (type) ANOVA for drift rate or simple one-way ANOVAs for the remaining model parameters (boundary, nondecision time, starting point). Generalized eta squared (η^2_G) is reported as a measure of effect size for the F tests.

Results

In order to ensure that the analyses were not unduly influenced by extreme scores, before any inferential analyses were conducted, we removed any RT that was faster than 300 ms or slower than 8,000 ms because these trials were likely fast guesses or attentional lapses, respectively. Any RT that was greater than 3 standard deviations away from the participant level mean was also removed. This trimming procedure removed 2% of the total number of trials.

Accuracy analyses. The means for each group and condition are presented in Table 2. As expected, recognition accuracy was significantly higher for low-frequency words than high-frequency words, $F(1, 78) = 90.47$, $p < .001$, $\eta^2_G = .17$. More important, there was a significant main effect of group, $F(1, 78) = 4.25$, $p = .04$, $\eta^2_G = .043$, indicating lower accuracy for family history+ participants. The interaction between frequency and family history was reliable but quite small, $F(1, 78) = 4.84$, $p = .03$, $\eta^2_G = .01$, indicating a larger effect of family history for low-frequency items as expected based on Balota et al. (2002).

RT analyses. The mean RTs for high- and low-frequency hits and correct rejections are presented in Table 3. Both the main effects of word frequency, $F(1, 78) = 42.8$, $p < .001$, $\eta^2_G = .012$, and word type, $F(1, 78) = 10.14$, $p = .002$, $\eta^2_G = .03$ were reliable, indicating faster responses to low-frequency items and to old items. However, there were few differences in the overall responses latencies as a function of family history. Specifically, the main effect of family history was not significant, $F(1, 78) < 1$, $p = .97$, $\eta^2_G = 0$, and none of the higher order interactions reached statistical significance.

The standard analyses were straightforward and quite in line with our expectations. Low-frequency items were responded to more quickly and accurately than high-frequency items. More important for the present work, our analyses revealed a significant effect of family history on recognition accuracy. However, as mentioned, the examination of accuracy and RTs alone do not provide a complete understanding of underlying cognitive mechanisms. The key strength of the diffusion model is to combine accuracy and RT information into latent parameters that reflect underlying cognitive processes. We now turn to a discussion of these analyses.

Diffusion model analyses. Diffusion model estimates for the individual participant raw data were obtained using the fast-dm program developed by Voss and Voss (2007). This program recovers the optimal model parameters by minimizing the maximum distance between the empirical cumulative distribution function (CDF) and the CDF predicted by the model. There are other methods of recovering model parameters. It is important to note that in a simulation study, Ratcliff and Childers (2015) showed that even with 40 trials per condition, the parameters recovered by fast-dm correlated ~.6 with the parameters that were used to simulate the data. These correlations were similar to or better than other publically available fitting methods. The upper response boundary was designated as "old" responses and the lower boundary was designated as "new" responses. All parameters, including across trial variability in the parameters (nondecision time, drift rate and start point), were constrained to be constant across the

Table 2
Recognition Accuracy (Means and Standard Deviations) as a Function of Family History in Experiment 1

	HF d'		LF d'	
Family history	*M*	*SD*	*M*	*SD*
Negative	2.05	0.66	2.75	0.69
Positive	1.91	0.60	2.35	0.51

Note. HF = high frequency; LF = low frequency.

Table 3
Response Latency in Milliseconds (Means and Standard Deviations) as a Function of Family History in Experiment 1

	HF hits		LF hits		HF CRs		LF CRs	
Family history	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Negative	1,052	326	978	266	1,182	387	1,140	392
Positive	1,111	310	1,006	204	1,140	236	1,087	183

Note. HF = high frequency; LF = low frequency; CR = correct rejection.

experimental manipulations (e.g., word frequency) with the exception of the drift rate.

Inferences that are drawn from a diffusion model analysis depend critically on how well the parameters recovered by the model accurately capture the empirical data. Following Ratcliff et al. (2004), we assessed model fit by calculating the empirical .1, .3, .5, .7, and .9 quantiles for correct responses and determining how closely they match the same quantiles predicted by the model. Figure 2 illustrates the model fit separately for the family history negative participants (see left column) and the family history positive participants (see right column) for each of the conditions. The markers and standard error bars represent the empirical quantile averaged across all participants in that group. The line represents the quantile that is predicted by the model parameters. As shown in the Figure, overall the model did an excellent job of capturing the observed data with only some misfit in the .9 quantile, which also tends to be the most variable. The model predicted and observed accuracy is also listed within each graph. It is important to note that there does not appear to be systematic differences in model fit across the two groups.

Table 4 displays the resulting, best fitting diffusion model parameters as a function of family history and frequency, separately for each type of item (e.g., old vs. new). For drift rate, there was a significant main effect of frequency, $F(1, 78) = 82.54$, $p < .001$, $\eta_G^2 = .08$, and a main effect of type, $F(1, 78) = 66.83$, $p < .001$, $\eta_G^2 = .26$, which together indicates drift rates were greater for low-frequency items as well as for new items. More important, there was a significant main effect of family history, $F(1, 78) = 6.5$, $p = .01$, $\eta_G^2 = .03$, indicating a lower drift rate for the family history+ participants than family history− participants. There was a single higher order interaction between word type and word frequency, $F(1, 78) = 15.97$, $p < .001$,$\eta_G^2 = .02$, indicating a larger frequency effect for old items.

Finally, simple univariate ANOVAs on the remaining model parameters indicated no reliable effect of family history on boundary, $F(1, 78) < 1$, $p = .98$, $\eta_G^2 = 0$, on starting point, $F(1, 78) = 1.49$, $p = .23$, $\eta_G^2 = .02$, or on nondecision time, $F(1, 78) < 1$, $p = .88$, $\eta_G^2 = 0$. These findings suggest group differences in recognition accuracy were isolated entirely to changes in the drift rate parameter.

We also tested for group differences in the variability parameters of the model. There was no effect of family history either on drift rate variability, $F(1, 78) < 1$, $p = .712$, $\eta_G^2 = 0$, nor on nondecision time variability, $F(1, 78) < 1$, $p = .374$, $\eta_G^2 = .01$. There was, however, a reliable difference on starting point variability, $F(1, 78) = 8.05$, $p = .006$, $\eta_G^2 = .09$.

Sensitivity of drift rate to family history. Although the diffusion model is important in that it provides information about the mechanisms underlying the family history effect, we were also interested to see if the estimates from the model provide any increased sensitivity compared with standard neuropsychological measures. To address this question, we conducted a stepwise logistic regression predicting family history status. In the first step of the analysis we entered performance on one of the neuropsychological tests (i.e., Selective Reminding, associate learning, delayed recall, Trails A and B, or Letter Number Sequencing). In Step 2 of the analysis we entered the average drift rate from the recognition test. We report the odds ratio as a measure of effect size.

After controlling for selective reminding performance, the drift rate significantly predicted family history status ($\beta = -.81$, $p = .036$, odds ratio = 2.24). Similarly, drift rate was significant after controlling for associate learning ($\beta = -.90$, $p = .026$, odds ratio = 2.45) and also delayed recall ($\beta = -.87$, $p = .022$, odds ratio = 2.38). In contrast, after controlling drift rate, none of the memory tests were significant predictors (selective reminding: $\beta = -.03$, $p = .47$, odds ratio = 1.03; associate learning: $\beta = .09$, $p = .76$, odds ratio = 1.09; delayed recall: $\beta = -.09$, $p = .767$, odds ratio = 1.09). Thus, there does appear to be unique information provided by the drift rate parameter that is not captured by episodic memory ability indexed by the standard neuropsychological tests we had available on this cohort. In addition, the effect of the drift rate remained significant above and beyond all the remaining neuropsychological tests on this cohort, including Letter Number Sequencing and Trails A and B ($ps < .05$).

Discussion

We replicated the finding that the effect of word frequency can be accommodated entirely by changes in the drift rate (Ratcliff et al., 2004). More important, the results yielded a clear effect of family history on accuracy and when the diffusion model was applied to the full set of data, the family history effect was captured entirely by differences in the drift rate parameter. Indeed, the other model parameters were quite similar across groups. These differences appear to reflect a relatively pure effect of family history, as all participants were APOE negative.

The drift rate parameter has strong relationships with overall cognitive ability as well as task difficulty (e.g., the frequency effect). These analyses indicated that not only can the influence of family history be detected on a sensitive cognitive measure but that it also can be isolated to a specific component of cognitive processing. Before discussing these results further, we now present an analysis of a second recognition experiment from a partially overlapping cohort to assess whether this finding can be generalized to another episodic recognition task that was administered under quite different conditions. The second experiment also serves as a stringent test that the diffusion model can adequately describe task performance across multiple experimental conditions.

Experiment 2

Method

Participants. A total of 83 individuals, recruited from the same population as in Experiment 1, participated in Experiment 2. Forty-eight of these participants were included in analyses of

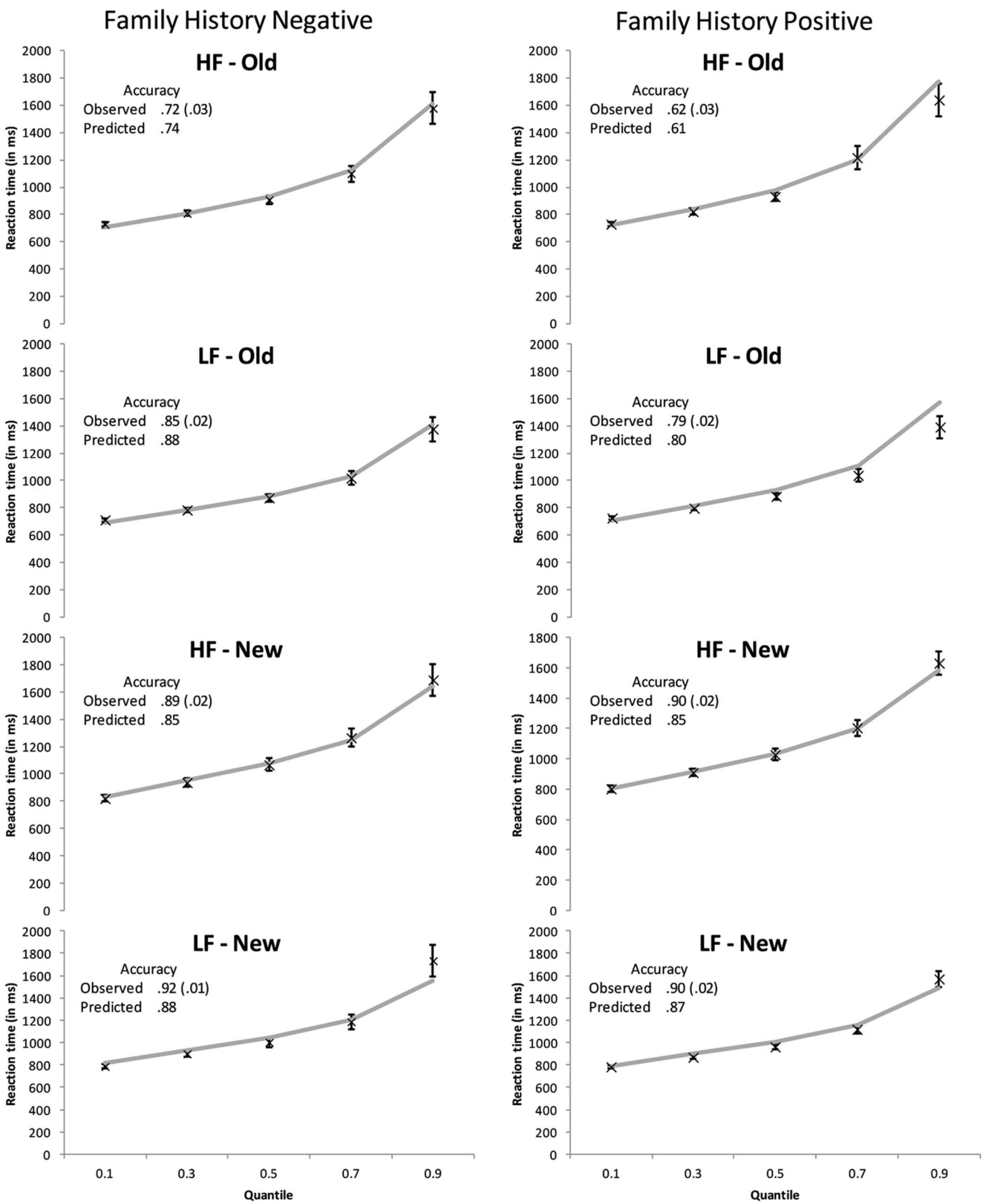

Figure 2. Empirical and model predicted quantiles and accuracy for Experiment 1. The line represents the quantiles predicted by the diffusion model and the points and error bars represent those quantiles calculated from the data. HF = high frequency; LF = low frequency.

Table 4
Diffusion Model Parameters Means (Standard Deviations) for Experiment 1

	Drift rates			
Family history	HF old	LF old	HF new	LF new
Negative	0.92 (1.35)	1.92 (1.38)	2.35 (1.13)	2.64 (1.11)
Positive	0.22 (0.89)	1.26 (1.03)	2.18 (0.81)	2.52 (1.06)

	Boundary, nondecision, and bias		
	Boundary	Nondecision	Bias
Negative	1.80 (0.62)	0.63 (0.10)	0.64 (0.10)
Positive	1.79 (0.47)	0.63 (0.09)	0.61 (0.11)

	Variability parameters		
	Drift date	Nondecision	Start point
Negative	.91 (.38)	.17 (.11)	.16 (.14)
Positive	.88 (.38)	.15 (.10)	.27 (.19)

Note. Bias was calculated as the start point divided by the boundary separation. A value above 0.5 indicates a bias toward the top boundary (an old response in the current experiment), and within trial variability was set to 1. HF = high frequency; LF = low frequency.

Experiment 1; however, the experimental differences between the two tasks as well as the 35 unique participants in this cohort allowed us to make inferences about the stability of the findings from Experiment 1. Furthermore, the two experiments were separated by an average of 3 months. The demographic variables available on this sample are presented in the right panel of Table 1. All participants were rated as CDR 0 and there were no significant family history effects for any of the neuropsychological tests.

We removed one participant from all analyses due to an extremely low accuracy in both conditions of the recognition task ($d' = .23$ for high-frequency items and $-.02$ for low-frequency items). Because this individual did not have dementia (all participants were rated as CDR 0), the negative d' in particular suggests this person either was not trying or did not understand the task instructions.

Procedure. In contrast to Experiment 1, the study and test phases of this experiment were separated by approximately a one hour delay, and the study phase was conducted under incidental encoding conditions. Specifically, participants completed an animacy judgment task (e.g., is this object living or nonliving), within an fMRI scanner. The task included 96 high (mean log HAL frequency = 9.29) and 96 low (mean log HAL = 6.61) frequency items which were evenly split between animate and inanimate objects. Participants were instructed to make their animacy judgment as quickly and as accurately as possible. These words were later tested in an episodic recognition task presented after the completion of the fMRI scan, hence the relatively long one hour delay. Participants were not informed about the later surprise memory test.

During the test phase of the recognition task, participants received 384 test items for a yes/no recognition test. There were 48 items within each cell of word frequency, animacy, and old/new status. The following events occurred on each trial: (a) a fixation cross and the target word appeared simultaneously; (b) participants indicated whether they studied this item in the animacy task or not by pressing the "1" key to indicate an "old" item or the "2" key to indicate a "new" item; (c) participants rated the confidence of their response on scale from 1 (*low confidence*) to 5 (*high confidence*). There was no emphasis on speed in this task and participants proceeded to make judgments at their own pace.

Results

Accuracy analyses. Recognition accuracy was quantified using d' as before. In order to maximize the similarity to Experiment 1, we collapsed across the animacy dimension when conducting these analyses. The means for each group and condition are displayed in Table 5. The main effect of word frequency was significant, $F(1, 81) = 105.76$, $p < .001$, $\eta^2_G = .10$, indicating higher discrimination for the low-frequency items. The main effect of family history was not reliable, $F(1, 81) = 3.14$, $p = .08$, $\eta^2_G = .03$, although means were higher for the family history negative group. The interaction between frequency and group was not reliable, $F(1, 81) < 1$, $p = .83$, $\eta^2_G = 0$.

RT analyses. The mean RTs for each condition are presented in Table 6. As before, the main effect of word frequency was significant, $F(1, 81) = 14.28$, $p < .001$, $\eta^2_G = .003$, indicating faster responses to low-frequency words. The main effect of word type was also significant, $F(1, 81) = 67.33$, $p < .001$, $\eta^2_G = .10$, indicating faster responses to old items. The main effect of group was again not significant, $F(1, 81) = 3.31$, $p = .07$, $\eta^2_G = .03$, however for the means the family history− group were overall faster than the family history+ group. None of the higher order interactions reached statistical significance.

Diffusion model analyses. The model again described the data fairly well. The empirically derived and model-predicted quantiles and accuracy are displayed in Figure 3. The degree of fit is quite remarkable given that participants were not placed under explicit speeded instructions and the diffusion model was designed as a model of speeded decision making. Of course, it should be emphasized that the primary goal of this second experiment was to determine whether the same effects from Experiment 1 would generalize to an experiment that included a number of procedural changes, and any degree of model misfit would only serve to add noise to our parameter estimates and make any such generalization less likely.

The best fitting model parameters from this analysis are displayed in Table 7. The top portion of this table displays the average drift rates for each condition. The main effect of word frequency was again significant, $F(1, 81) = 84.08$, $p < .001$, $\eta^2_G = .05$, as was the main effect of type, $F(1, 81) = 13.75$, $p < .001$, $\eta^2_G = .08$, indicating the drift rate was higher for low-frequency items and for

Table 5
Recognition Accuracy (Means and Standard Deviations) for Experiment 2

	HF d'		LF d'	
Family history	*M*	*SD*	*M*	*SD*
Negative	1.39	0.51	1.73	0.54
Positive	1.18	0.50	1.54	0.57

Note. HF = high frequency; LF = low frequency.

Table 6
Response Latencies (in Milliseconds), (Means and Standard Deviations) for Experiment 2

	HF hits		LF hits		HF CRs		LF CRs	
Family history	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Negative	1,964	490	1,930	502	2,303	610	2,247	582
Positive	2,131	612	2,078	636	2,609	724	2,504	633

Note. HF = high frequency; LF = low frequency; CR = correct rejection.

new items. More important, as in Experiment 1, the ANOVA revealed a reliable main effect of family history, $F(1, 81) = 5.53$, $p = .02$, $\eta^2_G = .03$, indicating higher drift rates for family history− participants. The only higher order interaction that was significant was type by frequency, $F(1, 81) = 5.20$, $p = .03$, $\eta^2_G = .003$, which indicated a slightly larger frequency effect for old items.

Finally, no group differences emerged in the remaining model parameters including boundary, $F(1, 81) = 3.30$, $p = .07$, $\eta^2_G = .04$; nondecision time, $F(1, 81) < 1$, $p = .79$, $\eta^2_G = .001$; or start point, $F(1, 81) < 1$, $p = .44$, $\eta^2_G = 0$. Furthermore, there were no group effects on variability including drift rate, $F(1, 81) < 1$, $p = .422$, $\eta^2_G = .01$; nondecision time, $F(1, 81) < 1$, $p = .464$, $\eta^2_G = 0$; and starting point, $F(1, 81) < 1$, $p = .562$, $\eta^2_G = 0$.

Sensitivity to family history. We again conducted logistic regression analyses to determine whether our drift rate measure would predict family history status above and beyond general episodic memory performance as indexed by the additional measures available on these participants. As in Experiment 1, the drift rate was significant after controlling for SRT ($\beta = -1.83$, $p = .028$, odds ratio = 6.25) and associate learning ($\beta = -2.21$, $p = .018$, odds ratio = 9.09). The effect of drift rate was smaller after controlling for delayed recall ($\beta = -1.66$, $p = .055$, odds ratio = 5.3). It is important to note that none of these tests significantly predicted group membership after accounting for drift rate (*p*s > .36). Again, as in Experiment 1, the drift rate significantly predicted family history status above and beyond all additional neuropsychological tests (ps < .05).

General Discussion

Family history is a well-documented risk factor for the development of AD and has been shown to modulate the accumulation of AD biomarkers even in cognitively healthy individuals (e.g., Xiong et al., 2011). However, the influence of family history on preclinical cognitive outcomes is less clear, with many studies finding either no differences (Donix et al., 2010; Hayden et al., 2009; Johnson et al., 2006; Mosconi et al., 2007) or differences on particularly subtle cognitive measures (La Rue et al., 2008; Xiong et al., 2011). Even when group differences are detected, their relationship to underlying cognitive processes typically cannot be definitively established. For example, is a lower accuracy score due to a deficit in information processing or a bias toward outputting a particular response? Similarly, a slower average RT could be indicative of a slower rate of information processing (i.e., a decreased drift rate) or an increase in caution in responding (i.e., wider boundaries). The present study was designed to assess what specific mechanisms may underlie the observed performance differences as a function of family history, independent of the influence of APOE.

Across two episodic recognition tasks, we showed that group differences in episodic recognition were isolated specifically to the drift rate parameter. This is in contrast to cognitively healthy aging in which the dominant pattern is typically that older adults' exhibit increased response caution and nondecision time and yet their drift rates remain quite similar to younger adult controls (Ratcliff et al., 2004). This suggests that the declines in the drift rate observed here might be a unique signature of preclinical AD. Indeed, numerous studies have already linked drift rate to underlying cognitive abilities such as working memory capacity and general IQ (Schmiedek et al., 2007), suggesting that family history+ individuals indeed have subtle but detectable cognitive deficits relative to family history− controls. The effect size of this group difference was small, which was expected given that our participants were all cognitively healthy. The fact that a group difference in drift rate was statistically reliable across both experiments, which incorporated different designs, speaks to the robustness of this effect.

It is important to elucidate the mechanistic changes attributable to family history for two reasons. First, it is assumed that accumulating AD pathology causes a specific cognitive deficit, indexed by a change in the drift rate, which results in worse performance on cognitive tasks. However, it is possible that group differences may result from other processes such as increased response caution. As noted above, this is the general pattern underlying performance differences across young and older adults. These distinctions are critical not only for the establishment of AD risk, but also for evaluation of which cognitive assessments may be most sensitive to intervention. For example, if the effect of a particular drug is to clear amyloid from the brain, and presumably to increase drift rate, one may fail to observe effects on cognitive outcomes if the root cause of the initial deficit lies elsewhere in the cognitive system (e.g., decreased cautiousness in responding). Alternatively, it possible that gains from the administration of treatment can be offset by unexpected changes in other process components (model parameters) such as an increase in drift rate (leading to an increase in accuracy) accompanied by a decrease in caution (leading to a decrease in accuracy) with both changes lowering RT. The important point is that the diffusion model has the capability to discriminate among these possibilities.

Furthermore, diffusion model parameters appear to tap distinct neural mechanisms as they have been shown to rely on different neural substrates. For example, although findings tend to vary slightly from study to study, a recent review by Mulder, Van Maanen, and Forstmann (2014) suggests that the drift rate may rely on frontal-parietal regions including the dorsolateral prefrontal cortex, inferior frontal gyrus, anterior cingulate cortex and intraparietal sulcus. In contrast, boundary separation relies more on presupplementary motor areas in addition to anterior cingulate cortex.

These dissociations between model parameters and underlying brain regions afford the possibility that different model parameters might show differential sensitivity to functional connectivity or neural activation in brain regions that are preferentially affected by early-stage AD processes. Recent work has identified several frontal-parietal regions that over activate during a task and this over activation is correlated with levels of AD pathology. For example, Gordon et al. (2015) recently reported functional activity

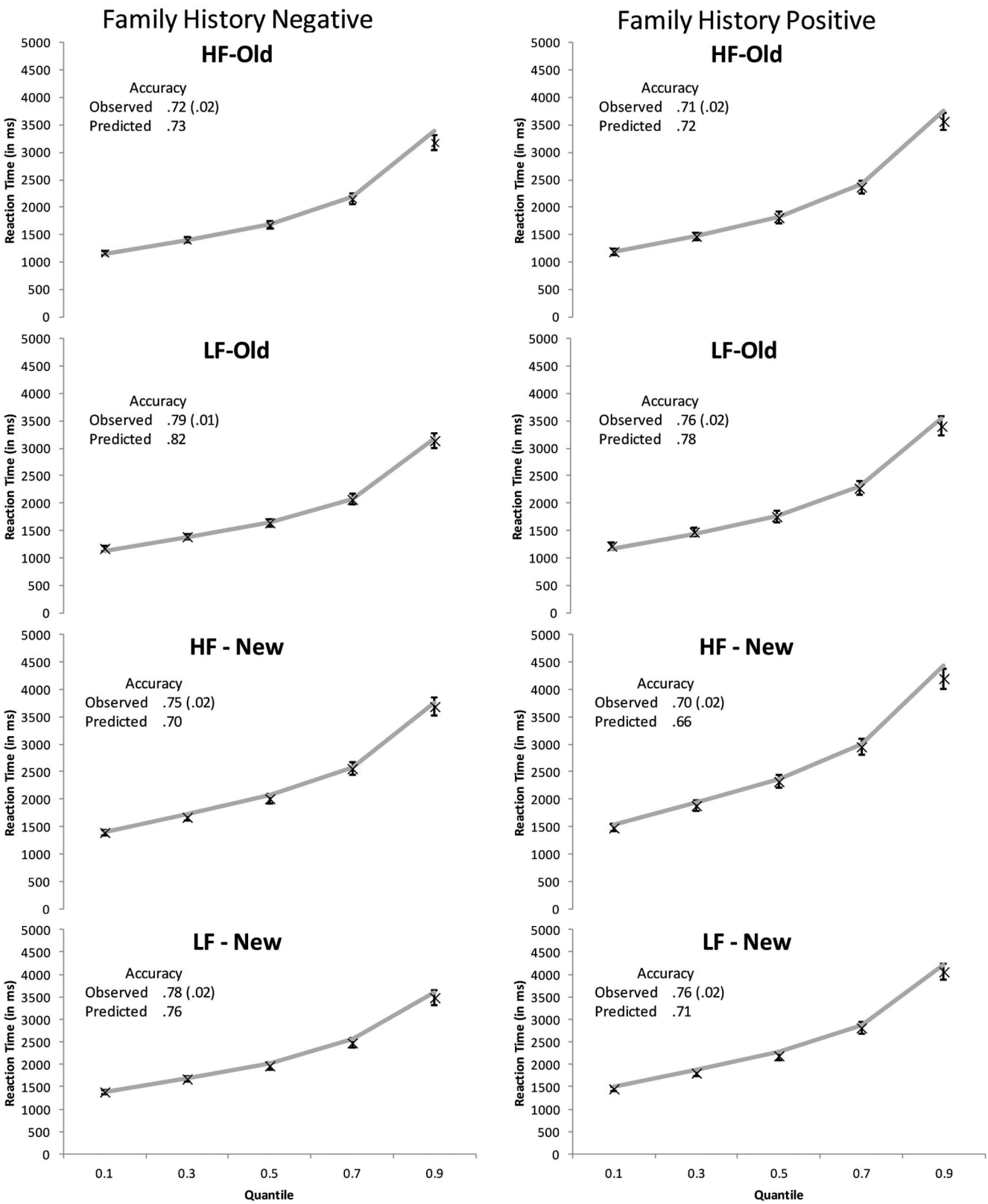

Figure 3. Empirical and model predicted quantiles and accuracy for Experiment 2. The line represents the quantiles predicted by the diffusion model and the points and error bars represent those quantiles calculated from the data. HF = high frequency; LF = low frequency.

Table 7
Diffusion Model Parameters Means (Standard Deviations) for Experiment 2

	Drift rates			
Family history	HF old	LF old	HF new	LF new
Negative	0.47 (0.54)	0.79 (0.46)	0.84 (0.50)	1.02 (0.53)
Positive	0.36 (0.37)	0.60 (0.47)	0.68 (0.50)	0.83 (0.51)
	Boundary, nondecision, and bias			
	Boundary	Nondecision		Bias
Negative	2.78 (0.61)	.93 (0.24)		.61 (0.09)
Positive	3.01 (0.56)	.95 (0.35)		.63 (0.10)
	Variability parameters			
	Drift rate	Nondecision		Start point
Negative	.68 (.20)	.33 (.30)		.25 (.17)
Positive	.64 (.24)	.28 (.29)		.27 (.16)

Note. Bias was calculated as the start point divided by the boundary separation. A value above 0.5 indicates a bias toward the top boundary (an old response in the current experiment), and within trial variability was set to 1.

in the dorsolateral prefrontal cortex, anterior cingulate and lateral parietal regions during an animacy encoding task was positively correlated with tau pathology in the cerebrospinal fluid. Mormino et al. (2012) showed that individuals with relatively high amyloid burden measured with PET-PIB exhibited greater task related activation across a set of brain regions that included the inferior frontal gyrus, a region that has been shown to correlate with drift rate (Mulder et al. 2014).

It is possible that these patterns of over activation reflect compensatory mechanisms in response to AD pathology elsewhere in the brain. Specifically, regions associated with the default mode network (DMN) have shown disruption due to high levels of amyloid pathology (Hedden et al., 2009; Sperling et al., 2009). Interestingly, internetwork correlations between the DMN and an attentional network that includes parietal regions identified above become smaller with increasing dementia severity (Brier et al., 2012). We believe that the present results support the contention that decision mechanisms captured by the diffusion model rely on a constellation of brain regions, many of which are impacted by increasing AD pathology that may not be captured by other behavioral outcomes such as accuracy. The complete delineation of cognitive processes represented by diffusion model parameters and underlying brain regions and pathology remain an important target for further research.

Second, this work is important from a measurement perspective in that different parameters may produce opposing effects at the level of average RT or total accuracy which would hinder the ability to detect overall group differences. For example, it is possible the family history+ group could offset their deficit in drift rate by increasing their boundaries which could eliminate the observed accuracy differences. Our analyses indicated that this was not the case. It is important to note that the diffusion model provides sensitivity to group or condition differences even when accuracy is very high. Ratcliff (2014) recently compared accuracy measures against drift rate to standard manipulations of difficulty across 11 basic perceptual tasks. The change in each measure as a function of increasing difficulty was often similar between (z transformed) accuracy and drift rate except when accuracy was very high. This was important in our data from Experiment 2, in which the group means in d' and response latencies did not differ, but joint consideration of RTs via the drift rate did produce a reliable difference.

Furthermore, the group differences in drift rate were not attributable to episodic memory assessed with standard neuropsychological tests including Selective Reminding Task, associate learning task or delayed recall tasks. In addition, the drift rate was significant after controlling for performance on the non-episodic memory based tasks that were available. This suggests these model parameters may have particular sensitivity to preclinical AD that is not detected by more standard tests. It is important to note that the memory tests examined here (associate learning and delayed recall) have demonstrated sensitivity to even very mild AD (e.g., Morris et al., 1991; Storandt & Hill, 1989); however, future work should also consider examining other measures of episodic memory performance.

We have referred to our group differences as the "effect" of family history. It is important to note that in the present study we are actually measuring the influence of various risk factors that are associated with a family history of AD. It is also important to note that the effects we have detected in the present study occurred in APOE negative individuals which raises the question of what risk factors family history is indexing. It is possible, and indeed likely, that family history is multifaceted and its effects could potentially arise from multiple mechanisms. In pursuit of this issue, we examined whether differences in other demographic variables that we had available might explain the behavioral differences that we observed. However, we found no group differences in levels of socioeconomic status, education, adverse cardiovascular events (e.g., heart attack), cerebrovascular events (e.g., stroke), or measures of personality from the NEO Five-Factor Inventory (Costa & McCrae, 1992).

It is also important to note that we also detected a difference in simple d' as a function of family history in Experiment 1. Thus, it is not necessarily the case that drift rate is providing unique information above and beyond signal detection in terms of group discriminability. Of course, signal detection models do not take into account response latency in helping to constrain our understanding of the nature of underlying cognitive mechanisms. Computational models, such as the diffusion model, are able to take into account all aspects of performance in order to isolate behavioral differences to specific components of cognitive processing. This is critical for further understanding the nature of cognitive deficits as a function of preclinical AD and AD risk.

It is interesting to consider the cross-experiment findings in the current study. Specifically, although there was some overlap in participants between the two studies, the same effects in drift rate were found across the two experiments, which were conducted on average 3 months apart, within a very different testing environment and with clear procedural differences. It is particularly intriguing that the results of Experiment 2 match those of Experiment 1 even without as much emphasis on speeded responses. This provides a very stringent test of whether the diffusion model can

capture episodic memory performance across quite different testing environments.

Our study has several limitations. First, although it is important that we established our effects are not confounded with APOE because all participants were negative for the ε4 allele, it is possible the current results will vary with genotype. Because of the small sample of ε4 positive, family history negative individuals, this would demand a much larger sample of participants to statistically address this issue. Second, our results are limited to a single task, namely episodic recognition. We are unable to determine whether these effects generalize to other binary decision tasks or are isolated specifically to episodic memory. Furthermore, the ACS cohort is a convenience sample and, thus, there could be subtle self-selection effects that might influence generalizability to a larger population of individuals with a family history for AD. Finally, this study was cross-sectional in nature and it will be important to demonstrate changes in a longitudinal study and provide links to underlying changes in the brain. Thus, the results presented herein represent a first step in a larger research program delineating the sensitivity of these novel measures of AD risk.

Conclusions

Taken together, our results add to the body of research implicating a role for family history as a risk factor for AD. It is important to note that our analyses extend this work by indicating subtle cognitive effects of family history are isolated to the drift rate, implicating a role of deficient information processing in these participants. These effects were found in the absence of APOE4 and were not attributable to general episodic memory performance indexed by several standard neuropsychological tests. This highlights the utility of sensitive cognitive indicators of preclinical AD and computational models of performance to better understand the mechanisms that are affected early in the disease course. These mechanisms may ultimately serve as more sensitive cognitive markers of AD risk or for the evaluation of treatment outcomes than overall accuracy or RT alone.

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