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Combining Attentional Control and Semantic Memory Retrieval: A Sensitive Marker for Early

Stage AD and AD-Related Biomarkers in Healthy Older Adults

by

Andrew J. Aschenbrenner

A thesis presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the
degree of Master of Arts

December 2013

St. Louis, Missouri

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ABSTRACT OF THESIS

Combining Attentional Control and Semantic Memory Retrieval: A Sensitive Marker for Early

Stage AD and AD-Related Biomarkers in Healthy Older Adults

by

Andrew J. Aschenbrenner

Master of Arts in Psychology

Washington University in St. Louis, 2013

Professor David A. Balota, Chair

Past studies have shown that measures of attentional control and semantic memory retrieval are sensitive markers of Alzheimer disease (AD). The present study examined the utility of combining measures of attentional control and semantic retrieval within a single task to discriminate healthy aging from early stage AD and show sensitivity to AD biomarkers in healthy control individuals. On each trial of the present task, participants viewed a category (e.g. "a unit of time") and verified whether a subsequent target item was an exemplar of the category ("hour") or not ("clock"). Importantly, the nonmembers of the category were associatively related (e.g., a "clock" is not "a unit of time", but is highly related), and hence, placed a premium on attentional control systems to reject. Results indicated that accuracy to the foil items was the strongest discriminator between healthy aging and very mild AD. Furthermore, accuracy correlated significantly with AD biomarkers, including tau, p-tau, $A\beta42$ and PIB, in healthy control participants who are at increased risk for developing Alzheimer disease. Discussion focuses on the combined influence of attentional control with explicit retrieval from semantic memory as a marker of early stage AD as well as a sensitive correlate of established biomarkers for AD risk in healthy control participants.

Introduction

There has been considerable research focusing on aspects of cognitive performance which can discriminate healthy aging from the earliest detectable stages of Alzheimer disease (AD). Indeed, it is now well established that AD-related changes are present in the brain long before the manifestation of overt cognitive symptoms (Morris et al., 1996; Price et al., 2009), suggesting a lengthy prodromal stage of the disease. Thus, it is critical to continue to explore markers that are indicative of this preclinical stage. Several such biological markers have already been identified. Specifically, the presence of at least one apolipoproteinE4 allele is a well-known genetic risk factor (Blacker et al., 1997), and more recently, changes in levels of Aβ42, tau and phospho-tau (p-tau) in the cerebrospinal fluid (CSF) have been shown to be sensitive preclinical markers (Diniz, Pinto Jr. & Forlenza, 2008; Fagan et al., 2007). For example, Fagan et al. (2007) reported levels of CSF tau and p-tau increase while levels of Aβ42 decrease in the earliest stages of AD. Finally, in addition to CSF markers, it is also possible to directly image amyloid plaques in the brain using Pittsburgh Compound-B (PIB), with AD patients exhibiting greater levels of PIB retention (Klunk et al., 2004), which in turn indicates greater AD-related amyloid deposition in patient brains. Importantly, both CSF measures and PIB have been shown to accumulate in non-demented older adults (Fagan et al. 2009, Mintun et al. 2006).

Although episodic memory impairment is considered the hallmark cognitive characteristic of AD, there is accumulating evidence of a breakdown in attentional control systems as well (Balota & Faust, 2001; Faust & Balota, 2007; Perry & Hodges, 1999; Twamley, Ropacki, & Bondi, 2006). Attentional control can be conceived of, in part, as maintaining task goals throughout an experiment and is particularly stressed when multiple, competing levels of information must be inhibited or controlled. For example, one well known paradigm for

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measuring attentional control is the classic Stroop task (MacLeod, 1991; Stroop, 1935). In this task, participants are asked to name the color of the ink a color word is printed in (e.g. the word RED printed in blue ink), rather than the word itself. The highly automatic "word" pathway competes with the task goal (naming the color) and must be controlled in order for the correct response to be made. Previous studies investigating Stroop performance in AD have shown intrusion errors to be particularly powerful in discriminating healthy aging from very mild AD and in predicting later conversion (Balota et al., 2010; Hutchison, Balota & Duchek, 2010; Spieler, Balota & Faust, 1996).

AD individuals also exhibit poorer performance on tasks of semantic memory relative to healthy controls, particularly when demands on attention are maximized. For example, AD individuals score lower on tests of category and verbal fluency and object naming (Canning, Leach, Stuss, Ngo & Black, 2004; Hodges, Salmon & Butters, 1992; Kirshner, Webb, & Kelly, 1984; Marczinski & Kertesz, 2006), in which participants must not only generate exemplars but also track which items have already been produced to avoid repetitions. Poor performance on this task may in part result from the attentional demands of explicit retrieval and avoiding repetitions. Furthermore, AD individuals show disrupted semantic priming under high attentional demands such as when the dominant meaning of a homograph must be inhibited (Balota & Duchek, 1991; Balota, Watson, Duchek, & Ferraro, 1999). Overall, these results indicate AD individuals are particularly affected when explicit semantic retrieval and/ or attentional control is required.

Cognitive Performance and AD Biomarkers

Research exploring the influence of accumulating CSF biomarkers (tau, p-tau and Aβ42) on cognition has been mixed. Nordlund et al. (2008) examined individuals with mild cognitive

impairment and showed participants with abnormal levels of both tau and Aβ42 performed slightly worse on tests of memory and attention compared to other MCI individuals with abnormal levels of only one biomarker (see also Ivanoiu & Sindic, 2005). Duchek et al. (2009) extended this work to cognitively normal individuals by investigating the effects of several AD biomarkers on performance in standard attentional control tasks (Stroop, Simon and task switching). Results indicated intra-individual variability in RT performance was reliably correlated with the presence of at least one ApoE4 allele and also to the levels of Aβ42 in the CSF in these non-demented older adults. In contrast to these experimental results, however, several other studies have shown little correlation between CSF markers and standard psychometric test performance (Fagan et al., 2009; Vemuri et al., 2009). Interestingly, Fagan et al. (2007) have shown that while the ratio of CSF tau to Aβ42 reliably predicts later conversion to dementia, the biomarkers in isolation do not.

Few studies have examined the relationship between PET PIB imaging and cognitive performance. Pike et al. (2007) reported a significant effect of PIB binding on an episodic memory composite score in healthy control individuals, but not with any non-memory domains. However, a subsequent report on a larger sample (Pike et al., 2011) found no relationship between PIB binding and any psychometric measures after controlling for age and education (see also Aizenstein et al., 2008; Storandt, Mintun, Head & Morris, 2009; Vemuri et al., 2011).

These findings suggest the relationship between biomarkers, cognitive performance and risk of AD conversion is complex, and perhaps only the synergistic effects of multiple biomarkers have any measurable impact on cognition. As the goal of AD research is to ultimately prevent symptomatic expression of the disease, it is important to understand the relationship between biomarkers and cognition in order to better predict risk of conversion.

Variability, Reaction Time Distributions, and Diffusion Modeling

Much of the previous research examining cognitive performance and AD risk factors has focused on measures of central tendency (i.e. mean level performance) on standard psychometric tests. It is possible that these measures simply lack the necessary sensitivity to detect prodromal changes in cognitive functioning due to concurrent AD pathology. Therefore, recent research has not only utilized more powerful tests of a specific psychological construct (e.g. the Stroop task) but has also begun to examine the subtle characteristics of reaction time distributions and measures of variability as potential indicators of AD risk. As already mentioned, IIV (as measured by the coefficient of variation) in RT performance has been shown to correlate with several of the biological markers of AD, including the ApoE4 allele, Aβ42 (Duchek et al., 2009) and white matter volume (Jackson, Balota, Duchek, & Head, 2012) suggesting increased trial to trial variability is indeed a sensitive marker of AD risk.

Although research into the cognitive underpinnings of IIV remains relatively scarce, there are several reasons to expect behavioral IIV is indicative of underlying pathology. For example, several studies have shown a relationship between IIV and both anatomical and functional brain changes, particularly in the frontal lobes (see MacDonald, Li & Backman, 2009 for a review). Interestingly, Kelly, Uddin, Biswal, Castellanos, and Milham (2008) showed increased IIV in a flanker task was related to disruptions in suppression of the default mode network (DMN: Raichle et al., 2001) as a function of task engagement. Specifically, participants who were less able to disengage the DMN during the task exhibited greater IIV in RT performance. This is intriguing as a marker of early stage AD because the DMN appears to be vulnerable to early amyloid deposition (e.g. Buckner et al., 2005; Sperling et al., 2009), and connectivity in this network has already been shown to correlate with behavioral measures from the Stroop task in

non-demented control individuals (Duchek et al. 2013). Thus, IIV is indeed showing promise as a cognitive marker of AD risk.

Extending beyond simple RT variability, other studies have explored changes in the characteristics of the entire RT distribution as a function of healthy aging and very mild AD. For example, Tse, Balota, Yap, Duchek and McCabe (2010) used ex-Gaussian analysis to explore how changes in the RT distribution manifest across healthy aging and early stage AD. The ex-Gaussian reflects the convolution of two underlying distributions; a Gaussian with the mean and standard deviation reflected by Mu and Sigma parameters, and an exponential, reflected by a single parameter, Tau. There is clear evidence that these parameters can be decoupled by different experimental manipulations (Balota & Yap, 2011; Heathcote, Popiel, & Mewhort, 1991), and the results from Tse et al. (2010) indicated that healthy aging influenced all three parameters, whereas early stage AD primarily influenced Tau which is related to the slow tail of the reaction time distribution.

Finally, the measures discussed above are simply describing changes in the shape of the RT distribution, and currently there is no explicit model of why these changes occur. Consider the well-known speed accuracy tradeoff as an example. In tasks such as episodic recognition, older adults often show very little deficit in accuracy but are much slowed in response latencies (e.g. Ratcliff, Thapar & McKoon, 2004). That is, the older participants may slow down overall in order to maintain a desired level of accuracy. Examination of simple mean RTs (or even components of the ex-Gaussian) do not directly speak to this issue. Thus, while it is clear that AD participants exhibit more distributional skewing overall (Tse et al. 2010), it is unclear *why* this is the case. Therefore, an important step is to apply a computational model of cognitive

performance in these populations to isolate specific and psychologically interpretable parameter changes as a function of AD and AD risk.

One of the most widely used and influential models of binary decision making is Ratcliff's (1978) diffusion model. As illustrated in Figure 1, the diffusion model assumes noisy accumulation of evidence over time (the drift rate) towards a response boundary. A response is executed once sufficient evidence has accumulated to surpass the corresponding boundary. The distance between the two response boundaries reflects caution on the part of the decision maker. In other words, wider boundaries mean more evidence is required before a response is made. Other major parameters of the model include non-decision time, which includes processes that occur outside the decision process (e.g. motor execution), and the start point, which reflects bias towards once response option or the other. Most critically, the diffusion model is able to account for all aspects of performance including accuracy rates and RT distributions, perhaps providing the most sensitive measure of AD risk.

The diffusion model has been applied in studies investigating the effects of healthy aging in several cognitive tasks (Ratcliff, Thapar, & McKoon, 2010, 2011; Ratcliff, Thapar, Gomez, & McKoon, 2004). Interestingly, in the tasks used by Ratcliff and colleagues, healthy aging primarily influences non-decision time and boundary separation (older adults take longer to encode the stimuli and are overall more cautious), but typically not drift rate (the evidence entering the diffusion process does not lessen with age), whereas IQ primarily affects the drift rate parameter, but not the non-decision time or boundary separation parameters. Thus, the diffusion model appears to be a useful tool for separating the effects of aging on specific components of processing in binary decision tasks.

Figure 1. Major parameters of the Ratcliff (1978) diffusion model.
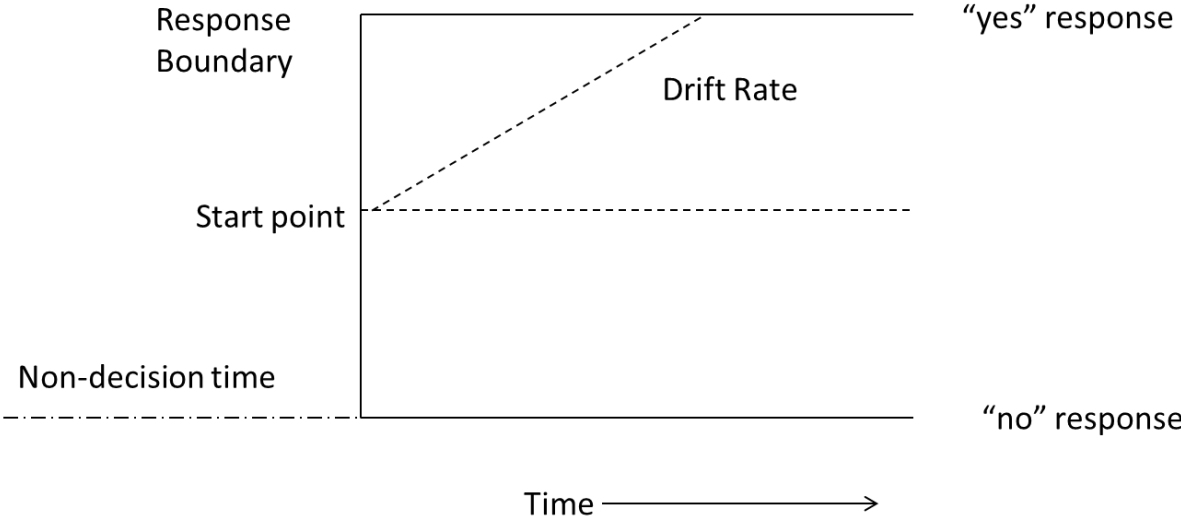
Regarding changes in early stage AD, one might expect the drift rate to be particularly sensitive to AD related cognitive changes given that the Tau component of the ex-Gaussian is highly related to drift (Matzke & Wagenmakers, 2009). However, simulation studies have shown that increased Tau can also reflect wider response boundaries (Matzke & Wagenmakers, 2009). Indeed, the increased distributional skewing in AD reported by Tse et al (2010) could be due to diminished drift rates, increased response caution, or both. Using the Stroop task once again as an example, AD participants could be increasing their response boundaries in light of the task difficulty, or they may be less able to inhibit the high salient yet irrelevant word information which would decrease their drift. This once again highlights the applicability of the diffusion model in understanding cognitive changes in healthy and pathological aging.

Most critically, with a sufficient number of trials, both the ex-Gaussian and the diffusion model can be fit to data from individual participants. Indeed, these parameters have remarkable stability and utility as measures of individual differences (Yap, Balota, Sibley, & Ratcliff, 2012), and are sensitive to a variety of measures including age and IQ (Ratcliff et al., 2010), working memory (Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007; Tse et al. 2010), vocabulary knowledge (Yap et al., 2012), and resting state functional connectivity (Duchek et al., 2013). Therefore, both the ex-Gaussian and the diffusion measures have the potential to not only isolate specific cognitive changes as a result of AD (i.e. evidence accumulation vs. boundary separation), but may also be sensitive to subtle biological changes such as the buildup of AD biomarkers in the CSF and amyloid deposition in the brain.

The Present Study

In the present study, we aimed to develop a particularly sensitive measure of cognitive breakdowns related to AD pathology and pre-symptomatic biomarker buildup by explicitly

manipulating the demands on two processes thought to be affected in very mild AD: semantic retrieval and attentional control. To this end, we utilized a semantic verification task (SVT) in which participants were presented with a category (e.g. "a unit of time") followed by a target item, and determined whether the target was a member of the given category. For each category, two target exemplars within the category and two associatively related words that were not in the category were chosen. The strength of the category or associative relationship was varied across targets such that for each category, one exemplar and one foil were strongly related to the category and the other two were weakly related. For example, if the category is "a unit of time" the strong exemplar was "hour", the weak exemplar was "month", the strong associate was "clock", and the weak associate was "schedule". Importantly, using associatively related lures places strong demands on the attentional control system, similar to the Stroop task. Based on the sensitivity of error rates in past studies of Stroop performance, (e.g. Balota et al., 2010; Duchek et al., 2013; Hutchison et al., 2010), one might expect accuracy, as opposed to response latencies to be a particularly sensitive measure. Specifically, in order to say no to "clock" as a unit of time, one must control the strong association between "clock" and "time", and hence, breakdowns in attentional control may produce an increase in error rates in this condition.

In summary, we expect the combination of explicit semantic retrieval and attentional control required in the SVT, particularly in the difficult associative condition, to be sensitive to AD related cognitive changes. The present dataset affords a unique opportunity to investigate the sensitivity of these measures to the buildup of biomarkers indicative of AD. In particular, we anticipate that accuracy rates and subtle RT measures will be particularly sensitive to the high attentional demands in the difficult associative condition, and to the buildup of biomarkers in healthy control individuals.

In pursuit of these goals, we report the results from three sets of analyses. The first set of analyses compares performance based on standard measures of mean reaction time and accuracy. The second set explores group differences on the more subtle RT characteristics including ex-Gaussian and diffusion model parameters. For both of these analyses, we will address the influence of healthy aging by comparing young adults, middle aged, young-old and old-old healthy adults using a 4(group) by 2(condition: category or associate) by 2(strength: strong vs. weak) mixed effects ANOVA, followed by a comparison of the effect of AD status by comparing a single healthy older adult group (YO and OO groups combined) with individuals with very mild AD using ANOVA. In order to minimize age differences in the AD comparisons, we only included healthy controls who were 65 or older in those analyses. Additionally, since category and associate items require different responses (i.e. "yes" vs. "no"), we also conducted follow up analyses of the theoretically motivated group by strength interaction separately for each condition. Finally, and most importantly, the third set of analyses examined the sensitivity of the SVT measures to accumulating AD biomarkers in our non-demented healthy control sample by employing a series of hierarchical regression analyses.

Method

Participants

A total of 402 individuals were recruited for this study; 30 young adults from the undergraduate psychology subject pool at Washington University, 305 healthy older adults and 67 individuals with very mild AD. All older adults were recruited from the Charles F. and Joanne Knight Alzheimer's Disease Research Center (ADRC) at Washington University. Participants from the ADRC were assessed for dementia using the Washington University Clinical Dementia Rating scale (CDR: Morris, 1993). The CDR assigns a rating of 0, 0.5, 1, 2 or 3 reflecting no,

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very mild, mild, moderate or severe dementia respectively. The CDR is based on a 90 minute clinical interview and is made without reference to performance on psychometric testing. The accuracy of this research group in diagnosing dementia has been very high (93% accurate) as confirmed by later autopsy (Berg et al., 1998). Because the present study focuses on the earliest stages of Alzheimer disease, we only included older adult participants who had a CDR rating of 0 or 0.5.

In order to fully characterize the influence of healthy aging on the SVT, we included four groups of participants in our analyses, young adults (YA, mean = 20.1, range = 18-22), middle aged (MA, mean = 54.5, range = 48-59), young-old (YO, mean = 68.1, range = 60-75), and old-old (OO, mean = 80.2, range = 76-92).

Psychometric Testing

All older participants were administered a standard psychometric test battery by an examiner who was blind to the individual's CDR score. The battery included the MMSE (Folstein, Folstein, & McHugh, 1975), a test of memory using the Selective Reminding Test (Grober, Buschke, Crystal, Bang, & Dresner, 1988), and the Letter Number Sequencing subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997). Visual-perceptual motor performance was assessed using Trail Making A (Armitage, 1946), and Animals Naming (Goodglass & Kaplan, 1983) was administered as a measure of lexical-semantic retrieval. A series of t-tests were conducted comparing test performance between our age-matched control sample (CDR 0 with ages 65 and greater) and the CDR 0.5s. Results confirmed the CDR 0.5 group performed worse on all psychometric tests ($ps < .05$). Statistical analyses were not conducted on the individual age groups of our healthy controls because the young adults were not administered the

psychometric battery. Table 1 provides demographics and the results from the psychometric tests.

Genotyping, CSF Measurement and PET PIB Imaging

Genotyping for ApoE alleles (ε2, ε3, and ε4) was available on 296 healthy adult controls (ε22 = 2, ε23 = 31, ε24 = 10, ε33 = 157, ε34 = 81 and ε44 = 15). Due to the small number of individuals for some of the allele groups, we collapsed into presence of at least one ε4 allele (ε4+, n = 106) or absence of any ε4 alleles (ε4-, n = 190). In addition, CSF biomarker information was available for 225 healthy adult controls and PIB imaging data was available for 174 participants (see Fagan et al., 2007 and Mintun et al., 2006 for a full description of these assessments).

Semantic Verification Task

Forty categories were selected to be used as stimuli in the SVT. As described previously, for each category, two target exemplars (Category condition) and two associatively related foils (Associative condition) were chosen, to make a total of 160 category-target pairs. Half of the items were strongly related to the category and half were weakly related. The exemplar items were based on the Van Overschelde, Rawson and Dunlosky (2004) category norms and the associate items were selected using the Nelson, McEvoy and Schreiber (2004) free association norms. A full list of materials is available from the authors upon request.

On each trial, the following events occurred: (a) a fixation cross was displayed in the center of the screen for 1000 ms; (b) the category label was displayed for 2000 ms; (c) a blank screen was displayed for 650 ms; (d) the target item was displayed until a response was made. Participants were instructed to press "p" on the keyboard if the target word was a member of the

Table 1. Psychometric test performance of the older adult sample.

Variable / Test	Middle Age			Young Old			Old Old			CDR 0.5		
	M	n	SD	M	n	SD	M	n	SD	M	N	SD
Age	55	55	2.8	68	180	4.1	80	69	3.7	74	67	7.6
Education	16	55	2	16	180	3	15	69	3	15	67	3
MMSE	29	55	1	29	179	1	28	69	2	27	67	3
Animal Fluency	23	55	6	22	179	6	18	69	5	16	67	6
Trail Making A	29	55	10	32	179	12	41	69	13	46	67	25
Letter Number Sequencing	12	54	3	10	162	3	9	63	2	8	57	3
Selective Reminding	48	55	0	48	178	0	48	68	1	44	64	7

category and "q" if not. The order of presentation of categories and targets was randomized anew

for each individual. Each session began with six practice trials during which feedback was

provided after incorrect responses only. Feedback was not provided during test trials.

Participants were encouraged to respond as quickly and as accurately as possible.

<div align="center">**Results- Analysis 1**</div>

To minimize the influence of outliers, individual's data were screened in the following

way. First, all response latencies faster than 200 ms and slower than 7000 ms were removed, and

of the remaining latencies, trials which exceeded 3 standard deviations from the individual mean

were also removed. This procedure resulted in the removal of 2% of trials for the YA, MA and

YO groups and 3% and 4% of the trials for the OO and very mild AD groups, respectively.

Although the OO and AD groups had significantly more trials excluded from analysis, this

procedure was necessary to avoid the undue influence of a very few extremely long RTs. In

addition, one healthy older adult had an extremely high number of errors (over 90%, which was

likely due to not having the key mapping correct) and was excluded from all subsequent

analyses. We first present the analyses on raw RTs, but then report the more important analyses

on the within participant z-transformed data, which controls for group related differences in

general slowing (see Faust, Balota, Spieler, & Ferraro, 1999).

Age RT Analyses. Mean correct response latencies as a function of age and condition

are presented in the top panel of Figure 2. The ANOVA on these RTs revealed main effects of

age, $F(3,330) = 33.9$, $p < .001$, $\eta^2_p = .235$, condition, $F(1,330) = 61.2$, $p < .001$, $\eta^2_p = .156$, and

strength, $F(1,330) = 221.5$, $p < .001$, $\eta^2_p = .402$. There were three lower order interactions that

were qualifed by a reliable three-way interaction. Specifically, there was an age by condition

interaction, $F(3,330) = 3.5$, $p = .015$, $\eta^2_p = .031$, an age by strength interaction, $F(3,330) = 3.3$, p

= .021, η^2_p = .029 and a condition by strength interaction, F(1,330) = 427.9, p < .001, η^2_p = .565. There was also a significant age by condition by strength interaction, F(3,330) = 13.7, p < .001, η^2_p = .111, however, as seen below this interaction did not reach significance after controlling for general slowing.

Age z-score Analyses. Turning to the more important z-score analyses, presented in Figure 3, the ANOVA revealed main effects of age, F(3,330) = 9.8, p < .001, η^2_p = .082, condition, F(1,330) = 121.1, p < .001, η^2_p = .268 and strength, F(1,330) = 379.8, p < .001, η^2_p = .535. There was a significant age by strength interaction, F(3,330) = 3.3, p = .022, η^2_p = .029, as well as a condition by strength interaction, F(1,330) = 1140.9, p < .001, η^2_p = .776. The age by condition interaction was not significant, F(3,330) = 1.5, p = .225, η^2_p = .013, and the three way interaction also did not reach significance, F(3,330) = .833, p = .477, η^2_p = .008.

AD RT Analyses. Mean RTs by group and condition are presented in the lower panel of Figure 2. The ANOVA revealed a significant main effect of group, F(1,273) = 25.5, p < .001, η^2_p = .085, condition, F(1,273) = 129.8, p < .001, η^2_p = .322, and strength, F(1,273) = 190.1, p < .001, η^2_p = .411. There were two lower order interactions which were qualifed by a three-way interaction. Specifcally, there was a group by condition interaction, F(1,273) = 18.6, p < .001, η^2_p = .064 and a condition by strength interaction, F(1,273) = 456.9, p < .001, η^2_p = .626. The interaction among group by condition by strength was marginally reliable, F(1,273) = 3.8, p = .054, η^2_p = .014, which again did not remain after controlling for general slowing.

AD z-score Analyses: Again, turning to the more important z-score analyses, the ANOVA indicated a significant main effect of group, F(1,273) = 21.3, p < .001, η^2_p = .073, condition, F(1,273) = 151.5, p < .001, η^2_p = .357, and strength, F(1,273) = 230.7, p < .001, η^2_p = .458.

Figure 2. Mean RTs as a function of group and condition. Error bars represent the standard error of the mean.
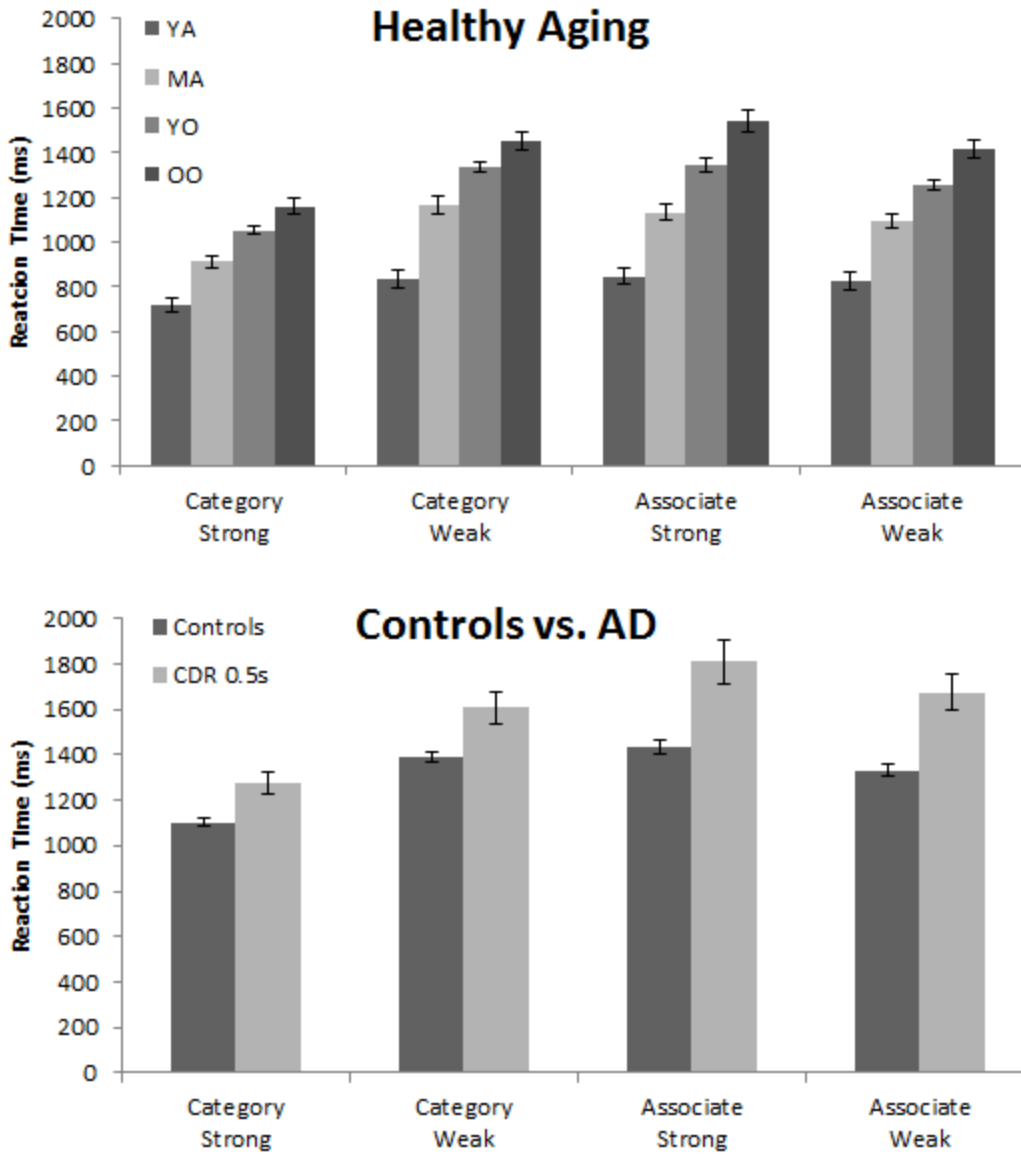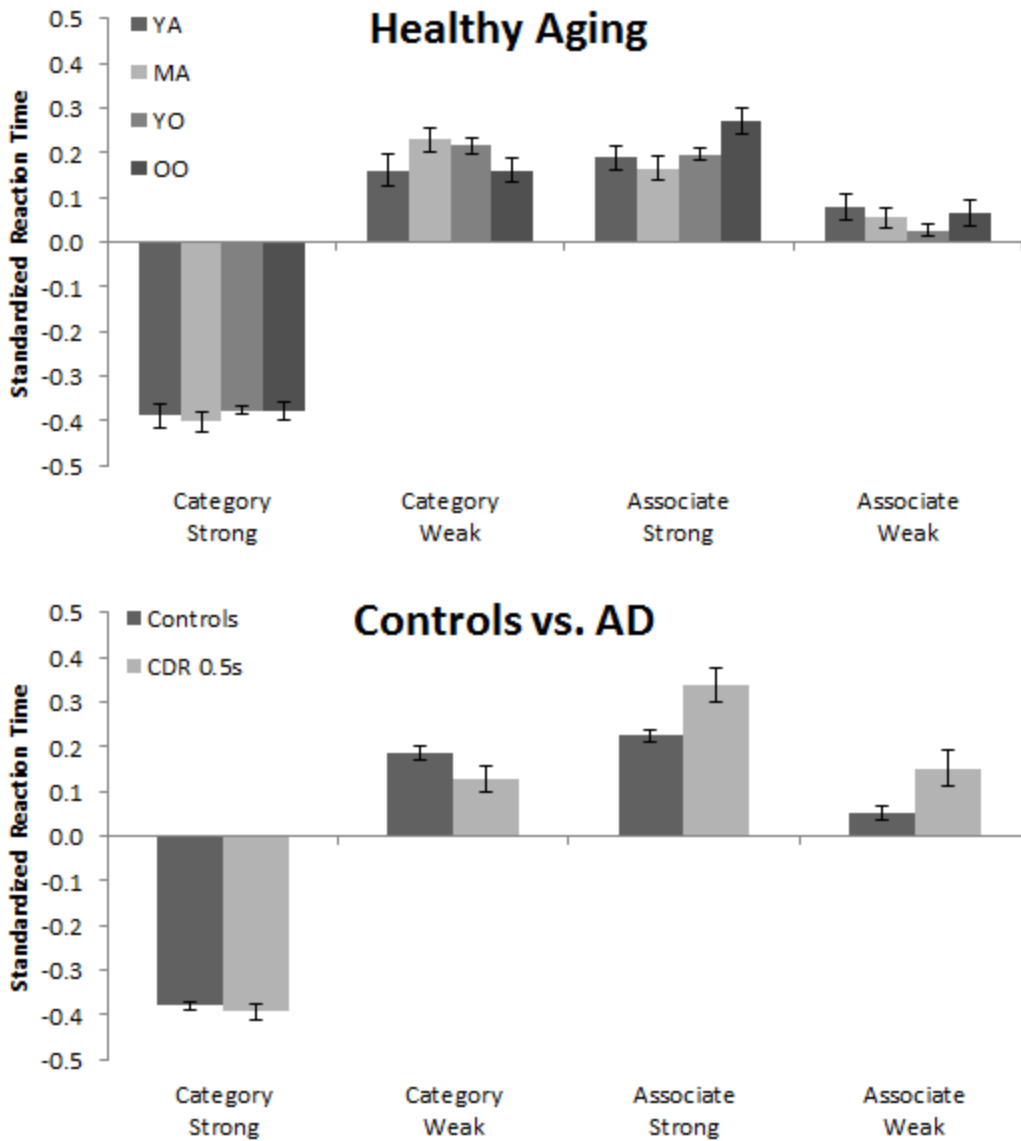
Figure 3. Mean z-scored RTs as a function of group and condition. Error bars represent the standard error of the mean.

There were two reliable lower order interactions. Specifically, the group by condition interaction was reliable, $F(1,273) = 8.3$, $p = .004$, $\eta^2_p = .03$ as was the condition by strength interaction, $F(1,273) = 942.1$, $p < .001$, $\eta^2_p = .775$. The three way interaction was not significant, $F(1,273) = .448$, $p = .504$, $\eta^2_p = .002$.

In summary, the results from the z-score analyses indicate that most of the robust effects of age and AD status on raw response latencies can be accomodated by the group related changes in general slowing, which further emphasizes the importance of controlling for overall processing speed across groups.

Age Accuracy Analyses. The mean percent correct is presented in Figure 4. The ANOVA revealed a significant main effect of age, $F(3,330) = 15.2$, $p < .001$, $\eta^2_p = .121$ and strength, $F(1,330) = 75.2$, $p < .001$, $\eta^2_p = .186$. There were two reliable lower order interactions that were qualified by a three-way interaction. Specifically, there was an age by condition interaction, $F(3,330) = 5.4$, $p = .001$, $\eta^2_p = .047$ and a condition by strength interaction, $F(1,330) = 625.9$, $p < .001$, $\eta^2_p = .655$. There was also a significant age by condition by strength interaction, $F(3,330) = 6.8$, $p < .001$, $\eta^2_p = .058$, which as shown in Figure 4 indicates that the old-old participants have particular difficulty in the associate strong condition.

AD Accuracy Analyses. The AD ANOVA revealed reliable main effects of group, $F(1,273) = 44.2$, $p < .001$, $\eta^2_p = .139$, condition, $F(1,273) = 36.0$, $p < .001$, $\eta^2_p = .117$, and strength, $F(1,273) = 17.0$, $p < .001$, $\eta^2_p = .059$. The group by condition interaction was highly reliable, $F(1,273) = 25.0$, $p < .001$, $\eta^2_p = .084$, as was the group by strength interaction, $F(1,273) = 7.4$, $p = .007$, $\eta^2_p = .026$, and the condition by strength interaction, $F(1,273) = 611.4$, $p < .001$,

Figure 4. Mean percent correct as a function of group and condition. Error bars represent the standard error of the mean.
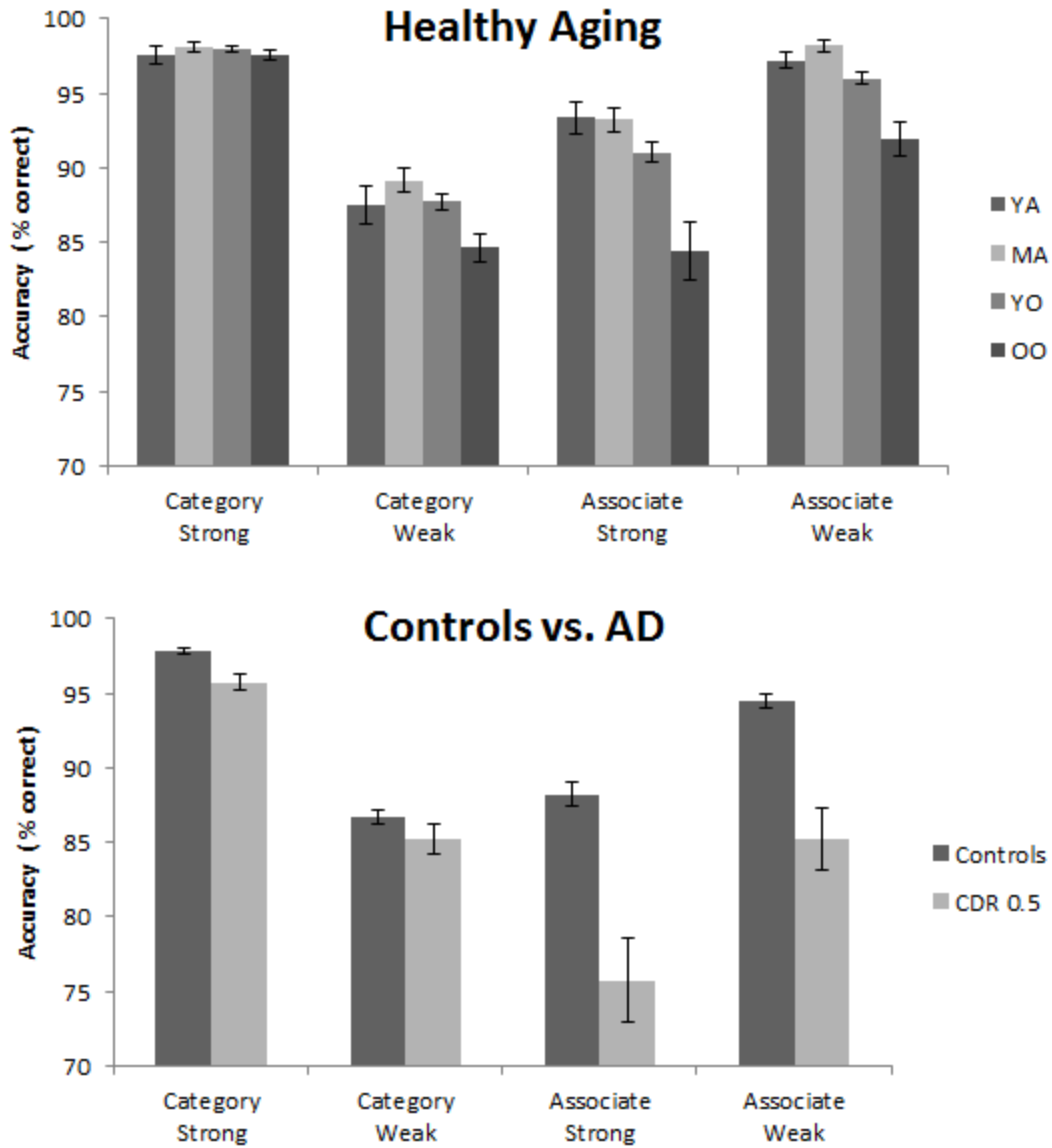
$\eta^2_p = .691$.

Finally, the interaction among group by condition by strength also approached significance, $F(1,273) = 2.9$, $p = .088$, $\eta^2_p = .011$. Follow up analyses indicated that the group by strength interaction for the category items was not significant, $F(1,273) = .418$, $p = .518$, $\eta^2_p = 002$, whereas this interaction was highly reliable in the associate condition, $F(1,273) = 8.6$, $p = .004$, $\eta^2_p = .031$. As predicted, it appears that the very mild AD participants have particular difficutly responding correctly to the strong associate items.

Interim Discussion

The results from the standard analyses are quite clear. First consider the effects of healthy aging. The results from the raw response latencies yielded large effects of condition and robust interactions among condition and group. However, the z-score analyses which control for group differences in overall response latencies, indicate that verification time is not disproportionately slowed with age. Specifically, all groups were equally slowed by the assoicate foils. This further emphasizes the importance of controlling for differences in general slowing. Although there were marginal effects of item strength for the associate items but not the category items, these indeed were relatively small after controlling for general slowing.

The accuracy data revealed a highly reliable age by condition interaction. Specifically, accuracy decreased with age, particucarly for the oldest adults. Furthermore, this relationship was modulated by the strength of the item, and this was particularly true for the associate items. This finding clearly suggests that the accuracy results appear to be more sensitive to age-related changes than the response latencies.

Turning to the effects of AD, the results from the raw response latencies again yielded a highly reliable interaction between group and condition. Although these effects diminished in the

analyses that controlled for general slowing, there continued to be evidence that the very mild AD participants were disproportionately slowed in responding correctly to the associatively related foils.

The results from the accuracy analyses were again quite informative. Importantly, the three-way interaction indicated that AD participants exhibited a larger effect of item strength in the associate condition but equal to the healthy controls in the category condition. Furthermore, the highly reliable group by strength interaction in accuracy to the associate items suggests that the AD participants are not simply more impaired at make a "no" response. Specifically, the familiarity signal from the strong associate items is very difficult to overcome and thus AD participants tend to respond incorrectly with a category "yes" response.

It is noteworthy that the pattern of response latencies and accuracy is similar to that reported by Spieler et al. (1996) using the Stroop color naming paradigm. Specifically, after taking into account overall speed differences, Spieler et al. (1996) reported AD participants exhibited an equivalent Stroop interference effect in RTs as the healthy controls. However, those same participants showed a large increase in intrusion errors (naming the word rather than the color), suggesting a greater influence of the word dimension in driving their incorrect prepotent response. Thus, accuracy measures appear to be particularly sensitive to early stage AD (also see Balota et al., 2010; Hutchison et al. 2010, Duchek et al, 2013).

Results-Analysis 2

We now turn to the more subtle measures in this dataset that we anticipated would also be particularly sensitive to AD status and AD related pathology in healthy controls. We present first the ex-Gaussian analysis of the RT distributions followed by the best fitting model parameters from the diffusion model. Ex-Gaussian parameters were obtained for each participant using

QMPE 2.18 (Cousineau, Brown & Heathcote, 2004; Heathcote, Brown & Mewhort, 2002), and diffusion model parameters were obtained using fast-dm version 29 (Voss & Voss, 2007). Because there was a maximum of 40 trials in each condition by strength cell, we collapsed across the strength dimension when conducting these analyses in order to avoid distorting the underlying distributions.

Age ex-Gaussian Analyses. Mean values of Mu, Sigma, and Tau are displayed in Figure 5. The ANOVA on the Mu parameter revealed a significant main effect of age, $F(3,330) = 31.3$, $p < .001$, $\eta^2_p = .222$, and condition, $F(1,330) = 104.8$, $p < .001$, $\eta^2_p = .241$, and a reliable interaction, $F(3,330) = 3.0$, $p = .031$, $\eta^2_p = .027$. Follow up analysis indicated this interaction was driven primarily by the OO group who exhibited increased interference relative to the younger groups (all $ps < .05$). No differences emerged among the other three groups. For Sigma, there was a main effect of age, $F(3,330) = 5.8$, $p = .001$, $\eta^2_p = .05$, and condition, $F(1,330) = 6.1$, $p = .01$, $\eta^2_p = .018$, and the age by condition interaction was marginal, $F(3,330) = 2.4$, $p = .068$, $\eta^2_p = .021$. For Tau, there was a significant main effect of age, $F(3,330) = 22.1$, $p < .001$, $\eta^2_p = .168$ and condition, $F(1,330) = 6.8$, $p = .01$, $\eta^2_p = .02$, but no interaction, $F(3,330) = 2.0$, $p = .119$, $\eta^2_p = .018$.

AD ex-Gaussian Analyses. Mean parameter values for the AD comparison are presented in Figure 6. For Mu, the main effects of group, $F(1,273) = 31.0$, $p < .001$, $\eta^2_p = .102$, condition, $F(1,273) = 111.4$, $p < .001$, $\eta^2_p = .29$, and the group by condition interaction, $F(1,273) = 23.2$, $p < .001$, $\eta^2_p = .078$, were all significant. This interaction indicates the CDR .5s are particularly slowed in the modal portion of their associate RT distribution. The results of the analyses for Sigma yielded a main effect of group, $F(1,273) = 25.9$, $p < .001$, $\eta^2_p = .087$, and

Figure 5. Mean ex-Gaussian parameters as a function of age and condition in the comparison of

healthy aging. Error bars represent the standard error of the mean.
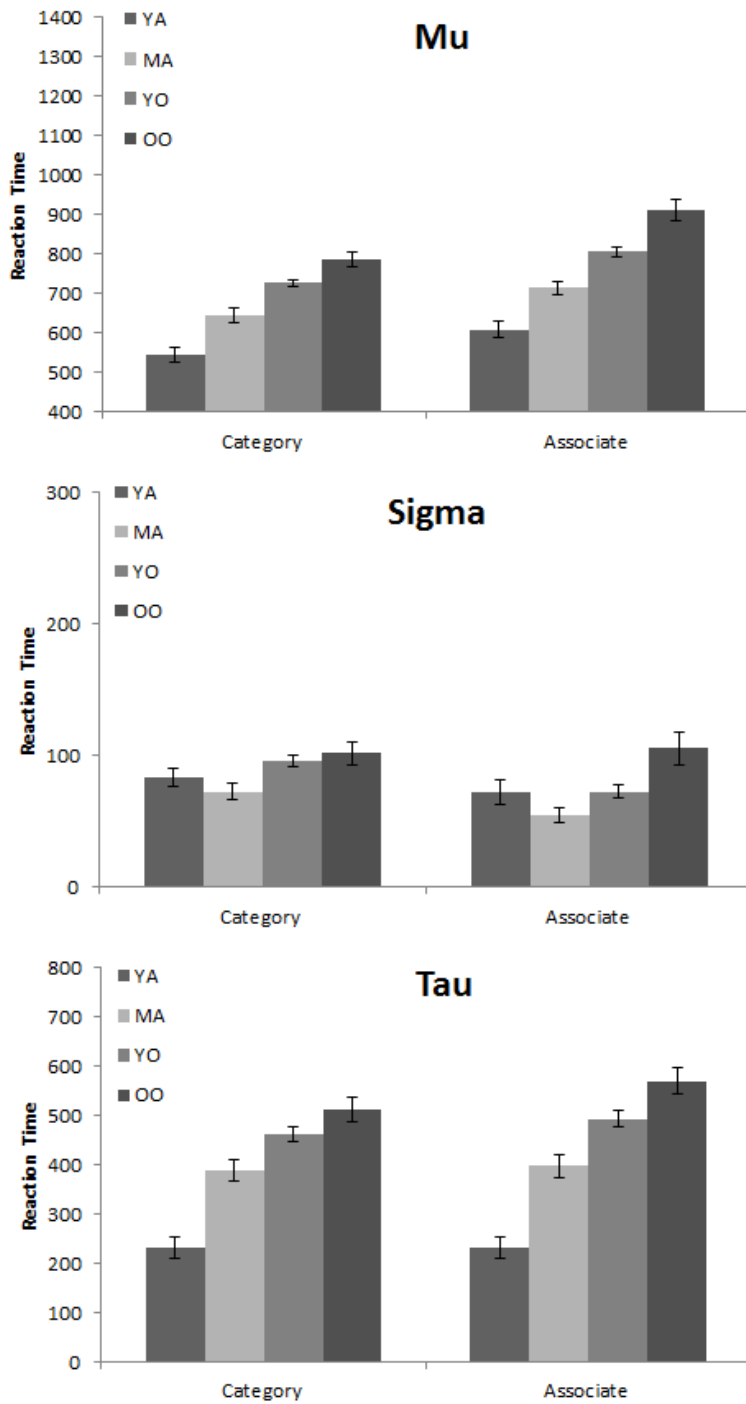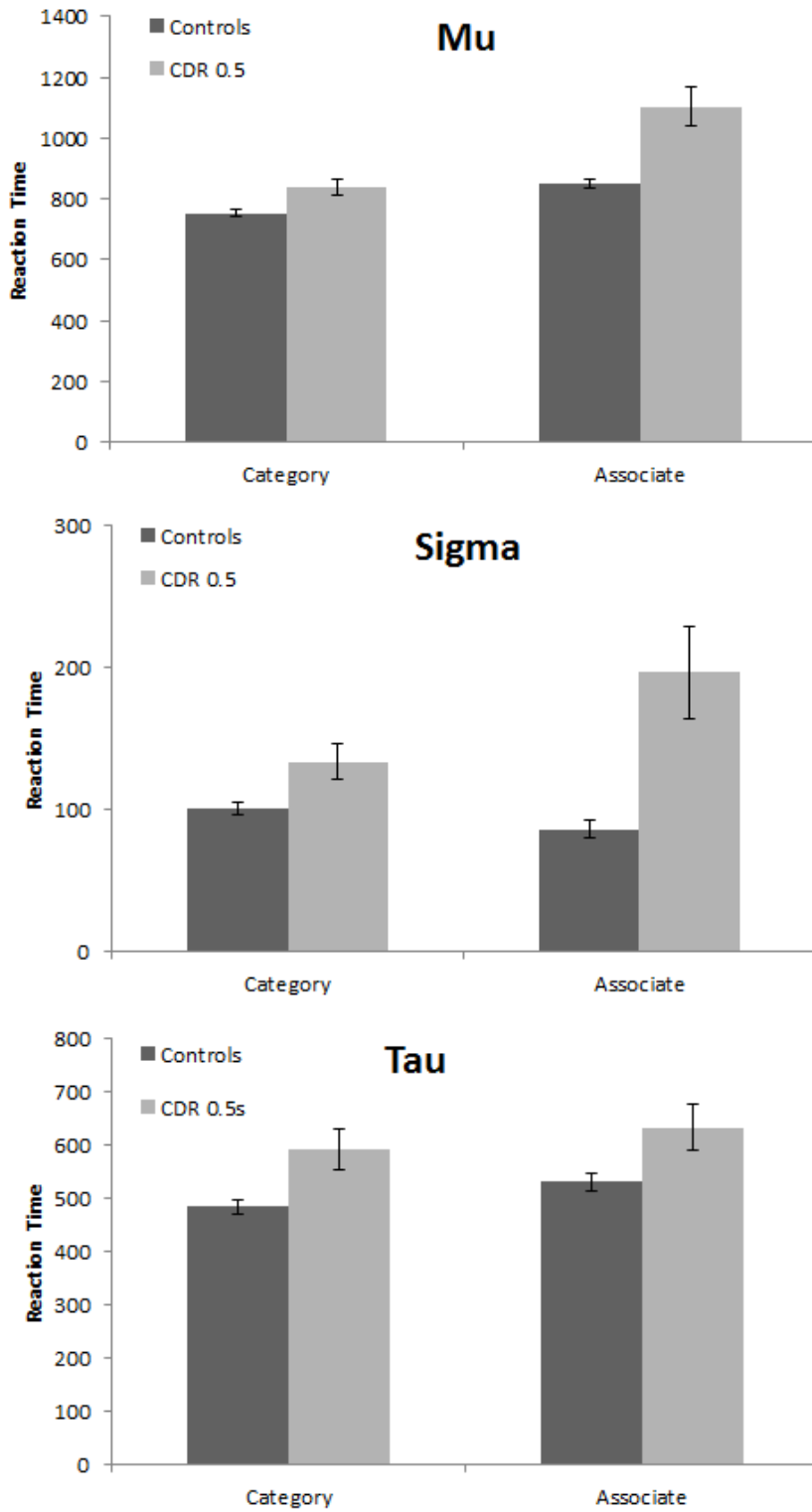
Figure 6. Mean ex-Gaussian parameters as a function of group and condition in the AD

comparison. Error bars represent the standard error of the mean.

condition, $F(1,273) = 6.8$, $p = .01$, $\eta^2_p = .024$, which were qualifed by a significant group by condition interaction, $F(1,273) = 17.4$, $p < .001$, $\eta^2_p = .06$. This interaction again indicates the CDR .5s to be much more variable in the associate condition relative to healthy controls. Finally, analysis of Tau revealed a main effect of group, $F(1,273) = 10.2$, $p = .002$, $\eta^2_p = .036$, and condition, $F(1,273) = 11.6$, $p = .001$, $\eta^2_p = .041$, but the interaction was not reliable, $F(1,273) = .01$, $p = .91$, $\eta^2_p = 0$.

Age Diffusion Model Analyses. Best fitting parameter values are displayed in Figure 7. There was a significant main effect of group on non-decision time, $F(3,330) = 20.4$, $p < .001$, $\eta^2_p = .156$, indicating encoding and motor execution processes increased with age. Turning to boundary separation, there was again a main effect of group, $F(3,330) = 17.4$, $p < .001$, $\eta^2_p = .133$, however, follow up pairwise comparisons indicated this effect to be driven by the YA group who set lower bounadries than all 3 older groups (ps < .01). The older groups did not differ from one another in regards to response boundary. Finally, the analysis of drift rates indicated significant main effects of group, $F(3,330) = 30.6$, $p < .001$, $\eta^2_p = .218$, condition, $F(1,330) = 114.4$, $p < .001$, $\eta^2_p = .257$ and a significant interaction, $F(3,330) = 14.5$, $p < .001$, $\eta^2_p = .116$. This interaction indicates the age related decrease in drift rates was larger for the associate condition than the catergory condition. Indeed, while associate drift rate consistently decreased across all age groups (ps < .01), the YA and MA groups did not differ in terms of category drift rate (p = .7) but had higher drifts rates compared to the two oldest groups (ps < .01).

AD Diffusion Model Analyses: Figure 8 displays the best fitting model parameters for the AD comparison. The ANOVA revealed a signifiant main effect of group on non-decision

Figure 7. Best fitting parameters from the diffusion model in the comparison of healthy aging.

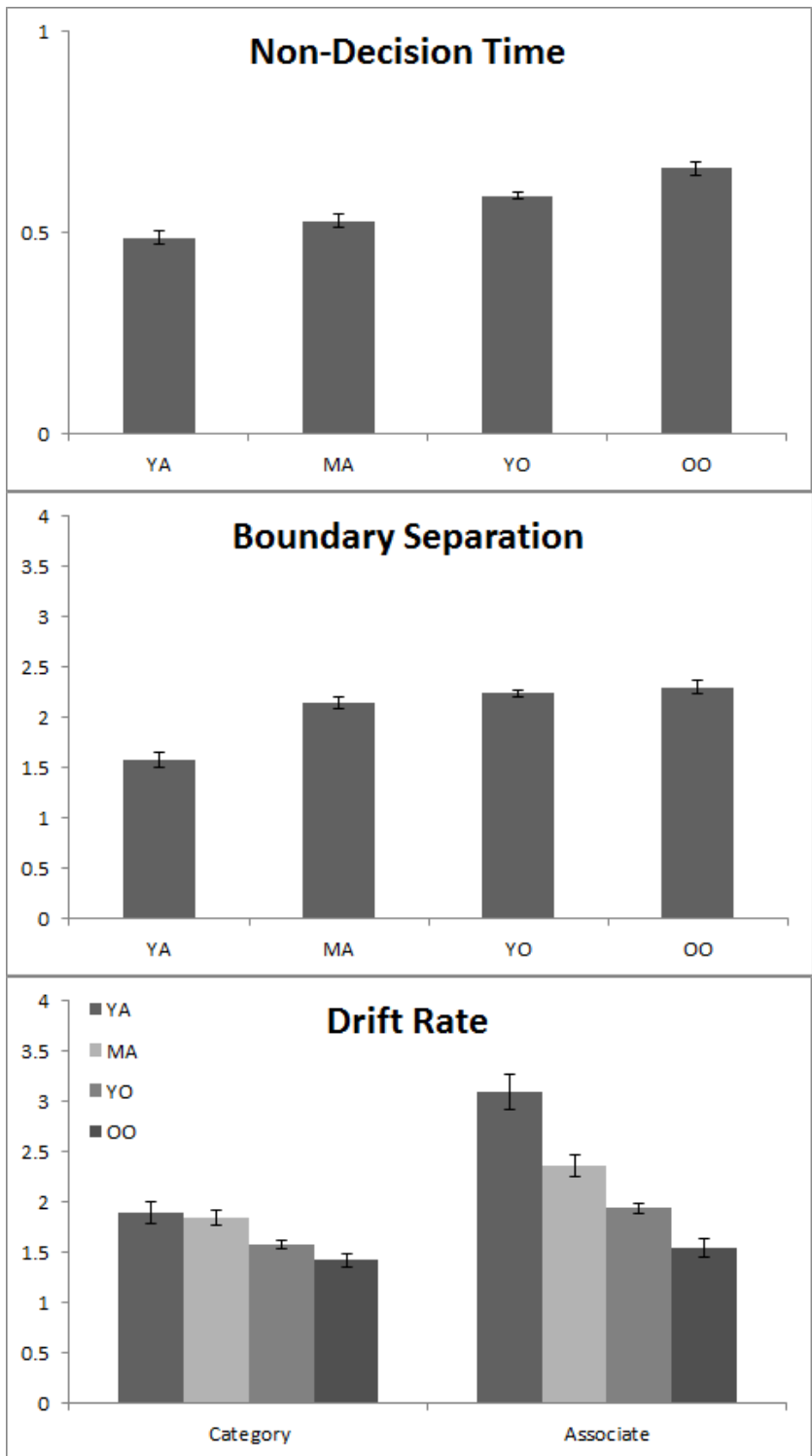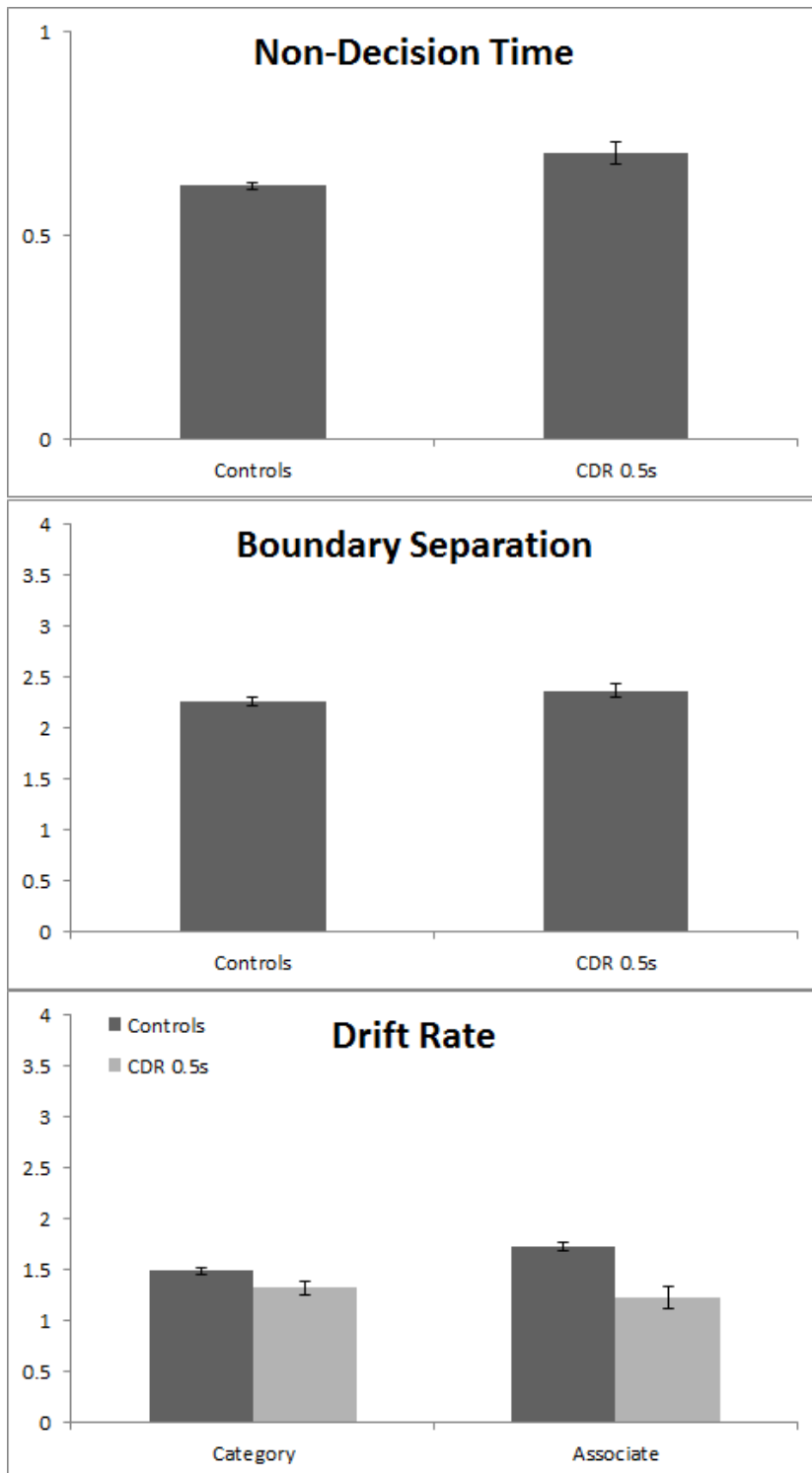Error bars represent the standard error of the mean.

Figure 8. Best fitting parameters from the diffusion model in the AD comparison. Error bars represent the standard error of the mean.

time, $F(1,273) = 13.9$, $p < .001$, $\eta^2_p = .048$, indicating longer non-decision times for the AD participants, however, the effect of group on boundary separation was not significant, $F(1,273) = 2.2$, $p = .139$, $\eta^2_p = .008$. Finally, the analysis of drift rate again revealed a significant main effect of group, $F(1,273) = 20.4$, $p < .001$, $\eta^2_p = ..07$, and a significant interaction, $F(1,273) = 7.6$, $p = .006$, $\eta^2_p = .027$, which indicates the AD related decrease in drift rate was larger for the associate condition than the category condition.

In summary, the ex-Gaussian analysis revealed several interesting findings. First, although both Mu and Tau were larger in the associate condition relative to the category condition, and all three parameters increased across groups, Mu but not Tau entered into interactions with group, both in healthy aging and in the AD comparison. One may have expected *a priori* an interaction to emerge in Tau, especially in healthy aging. Specifically, Spieler et al. (1996) demonstrated age-related increases in Stroop inference (incongruent – neutral) manifested entirely in Tau, whereas the increase was entirely in Mu for the AD participants. In the present data, age-related changes manifested primarily in the Mu parameter, however this was driven by the oldest-old group, which indeed replicates Spieler's et al. findings of a small effect in Mu for their oldest participants.

It is interesting that we did not observe an age related increase in interference for the Tau component. One possible explanation for this is the higher error rates in the associate condition, particularly for the older adult groups. Specifically, when one fails to control the prepotent response (i.e. makes an error), that trial is removed which would likely have ended up in the tail of the distribution. Indeed, this is one explanation for why AD-related increases in Stroop interference do not manifest in Tau (Spieler et al., 1996). However, inspection of the mean Tau interference for each group (YA = 0, MA = 7, YO = 31, OO = 58) suggests that the effect in Tau

actually increases across our age groups, and virtually no interference is present for the young adults.

An additional and potentially more interesting explanation for these findings is that the SVT encourages the use of certain attentional strategies to maximize performance. Specifically, in the semantic priming literature, it is generally accepted that priming effects at long SOAs can be modulated by two separate processes (Neely, 1991). The first process is prospective, by which after reading the prime, participants can generate an expectancy set of possible target items. If the subsequent target item is in the expectancy set, RTs are facilitated. Conversely, if the target is not in the expectancy set, one could see inhibition because presumably the expectancy set is searched first followed by a more general memory search. This type of processing is effortful and attention demanding. The second process is more retrospective, in which the participant waits for the target to appear then retrieves the prime word from memory in order to check for a relationship.

In the present task, the category label (e.g. "a unit of time") was displayed for 2000 ms before the target appeared. It is possible that healthy adults were able to use the cue to generate an expectancy set of possible target items or to actively direct their attention to the relevant area of semantic memory. For example, when presented with "a unit of time", they may activate specific exemplars such as "minute", "hour", etc. or they may simply prime the "time" area of memory. Thus, RTs are facilitated when the presented target is in the expectancy set because the target already has some measure of activation. On the other hand, when the target is NOT in the set, RTs are slowed, because a new memory search must be reinitiated after a search of the expectancy set is completed. Furthermore, this slowing should be restricted primarily to the tail of the RT distribution. Conversely, AD participants may not be actively generating an

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expectancy set, instead waiting for the target item (e.g. "clock") to prompt their memory search. Under this scenario, the differences between the category and associate conditions should be equal across the entire distribution.

We further explore this possibility by analyzing the distributional characteristics of the weak items only. These are items for which the familiarity signal will be minimized thus prompting a search through memory rather than making a familiarity based response. Recall that each condition by strength cell consisted of a maximum of 40 trials, which is likely too few to allow for stable ex-Gaussian estimation, so we instead performed an analysis of the quantiles. Specifically, the RTs were rank ordered and the .1, .3, .5, .7 and .9 quantiles were calculated and submitted to a 4 (age group) x 2 (condition: category vs. associate) x 5(quantile) for healthy aging or a 2 (group) x 2 x 5 ANOVA for the AD comparison.

The predictions are as follows: If all healthy adults are actively priming areas of semantic memory based on the category cue there should be no 3-way interaction among age by condition by quantile. Specifically, all groups should exhibit slowing of the category items relative to the associate items which should in turn be restricted primarily to the tail of the distribution. In contrast, if AD participants are not actively priming memory in response to the category cue, the second ANOVA should reveal this very interaction, and indeed these predictions were supported by the analysis. In the healthy aging comparison, the 3-way interaction was not reliable, $F(12,1320) = 1.0$, $p = .433$, $\eta^2_p = .009$, but in contrast, the 3-way interaction in the AD comparison was marginally reliable after correction for the violation of sphericity, $F(1.6,448) = 2.86$, $p = .069$, , $\eta^2_p = .01$. A follow up analysis of this interaction confirmed the quantile by condition interaction was highly reliable for the healthy controls ($p < .001$) but not for the AD

participants (p = .536). The quantiles are displayed in Figure 9. As can be seen, the interaction for healthy controls manifests primarily in the tail of the distribution precisely as expected.

In summary, these analyses converge on the idea that several distinct processes are in operation in the SVT. First, the accuracy data provide strong evidence for a fast, familiarity based decision. Specifically, in the associate condition, the high familiarity of the targets is very difficult to overcome which results in a disproportionate number of errors. Second, it is possible that healthy subjects are able to utilize the cue to proactively direct their attention to the relevant area of semantic memory, which generally speeds responses to category items. However, when the target is not in the set, RTs are slowed to those items because a more direct memory search must take place. This speculation is supported by the significant condition by quantile interaction (indicating the effect of condition increases across the quantiles) which doesn't itself interact with age. Therefore, the observed age differences in mean RT are likely due to processing speed differences in executing these component processes as indicated by the z-score analyses. On the other hand, the AD participants may not be engaging in this proactive memory process because our analysis indicated the difference between category and associate weak conditions was constant across the entire distribution. Of course, these conclusions are speculative and post hoc and would benefit from direct empirical testing, possibly by varying the SOA and including neutral items to determine whether speed differences are due to facilitation for the category items or inhibition of the associate items, or both.

A second interesting finding is that while our results show the expected age-related increase in all three parameters of the ex-Gaussian (e.g. Tse et al., 2010), we found all 3 parameters increased in AD as well, whereas results from Tse et al. indicate AD related changes occur primarily in Tau. This suggests a fundamentally different mechanism is operating in our

Figure 9. Quantiles of the associate and category weak items for healthy controls and very mild

AD individuals.
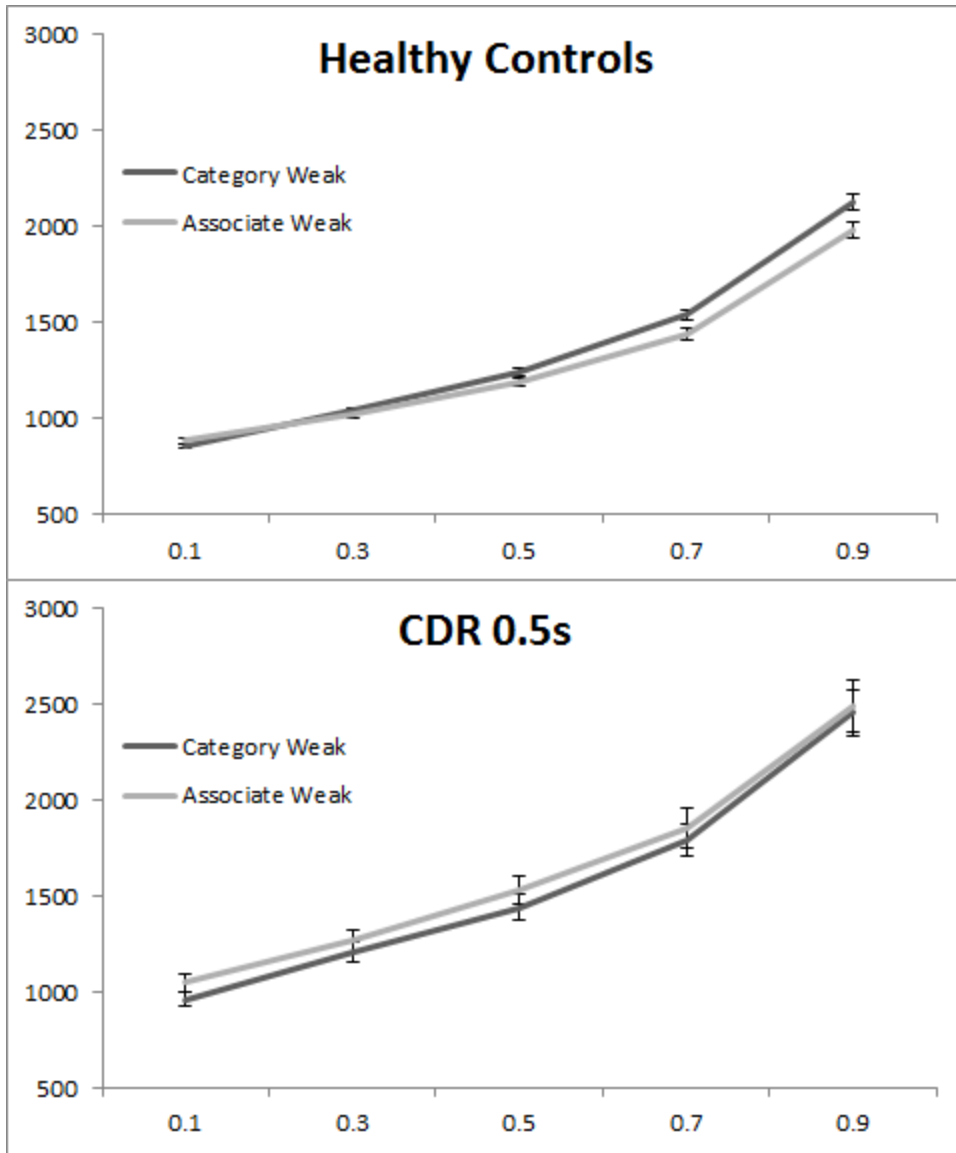
task which was not present in the standard attentional control tasks of Tse et al. One clear difference is the SVT requires an additional process of controlled search through semantic memory. We have argued that AD participants have difficulty prospectively directing attention to specific areas of memory based on the cue, which is indeed supported by the quantile analysis above. Of course, due to the nature of the foil items, it is impossible to completely separate semantic retrieval from attentional control in this task and indeed the combination of the two was expected to be particularly sensitive to AD pathology.

Finally, regarding the diffusion model analysis in the present data, and contrary to past research (e.g. Ratcliff et al. 2004), we found age related changes in the drift rates as well as in boundary separation and non-decision time. Specifically, older participants set wider boundaries and had longer non-decisions times compared to the younger participants, but also had lower drift rates, particularly in the associate condition. This implicates an age related reduction in the ability to control the highly salient associative information when making a response. Similarly to healthy aging, AD participants also had longer non-decision times and lower drift rate, which was again particularly pronounced in the associate condition. However, the AD participants set similar boundaries as the healthy controls.

As mentioned, the diffusion model assumes the accumulation of noisy evidence over time, which is reflected by the drift rate. The drift rate indicates the "quality" of evidence that is used to make the decision, although it is agnostic as to what this evidence consists of. Therefore, when responding to foil items, the associative information is causing the evidence to accumulate toward an upper (category response) boundary thus reducing the overall drift rate for those items. The pronounced decline in drift rate with aging and AD, suggests these participants are more susceptible to letting the associative information influence their response.

Results-Analysis 3

It is clear that performance in the SVT is very nuanced, yet the previous analyses clearly established that accuracy in the strong associate condition appears to be particularly sensitive to both age and AD status. In this light, we now turn to the primary goal of the present study and explore the sensitivity of the SVT measures to the buildup of biological markers of AD pathology in the non-demented CDR 0 participants. As noted earlier, there is accumulating evidence of changes in the CSF of healthy controls before the onset of cognitive symptoms of dementia can be detected. Hence, we examined whether the current measures would be sensitive to these biomarker changes in non-demented individuals. A series of Pearson product moment correlations were conducted between the biomarkers (tau, p-tau, Aβ42 and PIB) and each of the measures from the SVT (RT, accuracy, ex-Gaussian and diffusion parameters) in our entire sample of CDR 0 participants. Since both tau and p-tau are positively skewed we applied the natural log transformation to better approximate normality. Additionally, in order to avoid spurious correlations due to multivariate outliers, we first calculated Mahalanobis D^2 for each individual and eliminated any observation that occurred with a probability of less than .001. The procedure eliminated 5 participants from the CSF analyses and 2 participants from the PIB analyses. As noted previously, there are more participants for whom we have CSF data than PIB data, so in order to maximize power we conducted these analyses separately for CSF and for PIB. In these and all subsequent analyses, we partialed age, years of education and the difference between date of the biomarker assessment and cognitive testing. The final correlations are presented in Table 2.

There are several observations to note in the table. First, the accuracy in the associate condition correlates significantly with all four biomarkers. Specifically, accuracy increased with

increasing levels of Aβ42, and also decreased with increasing levels of tau, p-tau and PIB binding, which is exactly the pattern one would expect based on how these biomarkers accumulate in individuals at risk for developing AD (Fagan et al., 2007). Second, the response latencies, ex-Gaussian parameters and drift rate in the associate condition also appear to be sensitive to Aβ42 and /or PIB. Additionally, none of the measures from the category condition correlated with the CSF markers. Indeed, the only category measure that showed any sensitivity was the Mu parameter which correlated with PIB. Overall, this dissociation between the category and associate measures in regard to sensitivity to the biomarkers is striking and suggests that the high level of attentional control which is required to successfully reject the associatively related words can differentiate individuals who are at increased risk of developing dementia.

As mentioned previously, it is hypothesized that CSF tau and Aβ42 contribute to independent processes in the development of AD (Holtzman, Morris, & Goate, 2011; Storandt, Head, Fagan, Holtzman, & Morris, 2012). It is interesting in this regard that the associate accuracy correlates significantly with both of these markers and possibly to both processes of the disease. Given the theoretical importance of this possibility, we further explored the relationship between associate accuracy and CSF tau and Aβ42. First, we conducted a two-step hierarchical regression analysis predicting associate accuracy from age, education, date of test and CSF tau in step one, followed by Aβ42 in step two. All variables were standardized for these analyses. As expected, both tau (beta = -.184, p = .005) and Aβ42 (beta = .275, p < .001) were significantly related to accuracy. Furthermore, the R^2 change in the second step was highly significant (R^2 change = .073, p < .001), which indicates tau and Aβ42 account for independent variance in accuracy.

Table 2. Pearson correlations between measures on the SVT and AD biomarkers in healthy control participants.

|	Tau	Ptau	Aβ42	PIB
Category Accuracy	-.06	-.105	-.034	-.031
Associate Accuracy	-.149*	-.158*	.270**	-.297**
Category RT	-.001	.051	-.027	.11
Associate RT	.082	.123	-.137*	.275**
Category Mu	-.044	.022	-.08	.164*
Associate Mu	.039	.098	-.168*	.307**
Category Sigma	-.043	.033	-.06	.130
Associate Sigma	.086	.109	-.110	.164*
Category Tau	.034	.061	.019	.037
Associate Tau	.103	.124	-.083	.186*
Boundary Separation	.035	.053	.060	.086
Non-Decision Time	-.036	.02	-.165*	.188*
Category Drift	.083	.072	.074	-.038
Associate Drift	.042	.074	-.170*	.190*

Several studies have implicated the ratio of tau to Aβ42 in the CSF as being a particularly sensitive measure of AD risk (Duchek et al., 2009; Fagan et al., 2007). To further explore the possible synergistic relationship between the two variables, we conducted a second two-step regression analysis with all the predictors from our first analysis (including tau and Aβ42) entered in the first step and the interaction between the two biomarkers in the second step. The R^2 change in the second step (reflecting the contribution of the interaction) was significant (R^2 change = .02, p = .019), indicating tau is more strongly related to associate accuracy at different levels of Aβ42. A follow up test of the simple slopes (Preacher, Curran, & Bauer, 2006) indicated the effect of tau on accuracy was only significant at low levels of Aβ42 (beta = -.276, p < .001). At both average and high levels of Aβ42, the effect of tau was not significant (ps > .1). This interaction is plotted in Figure 10.

Finally, to examine the sensitivity of the associate accuracy to the presence of at least one ApoE4 allele, we conducted a final regression analysis predicting associate accuracy from age, education and ApoE4 status. The effect of ApoE status was significant (beta = -.307, p = .02) indicating lower accuracy for those individuals with at least one E4 allele. However, when the CSF markers tau and Aβ42 were also included, the effect of ApoE status was no longer significant (p =.425). Thus, there is no direct effect of ApoE status on SVT performance above and beyond the influence of the CSF biomarkers.

Comparing the Sensitivity of Associate Accuracy to Psychometric Measures

The present results suggest that associate accuracy from the SVT may be particularly sensitive to the accumulation of underlying pathology indicative of AD. As noted previously, the relationship between standard psychometric measures and AD biomarkers has been mixed. In order to further explore the specificity of associate accuracy to the biomarkers, we conducted a

Figure 10. Interaction between CSF tau and Aβ42 as related to associate accuracy.

Interaction between CSF Tau and AB42
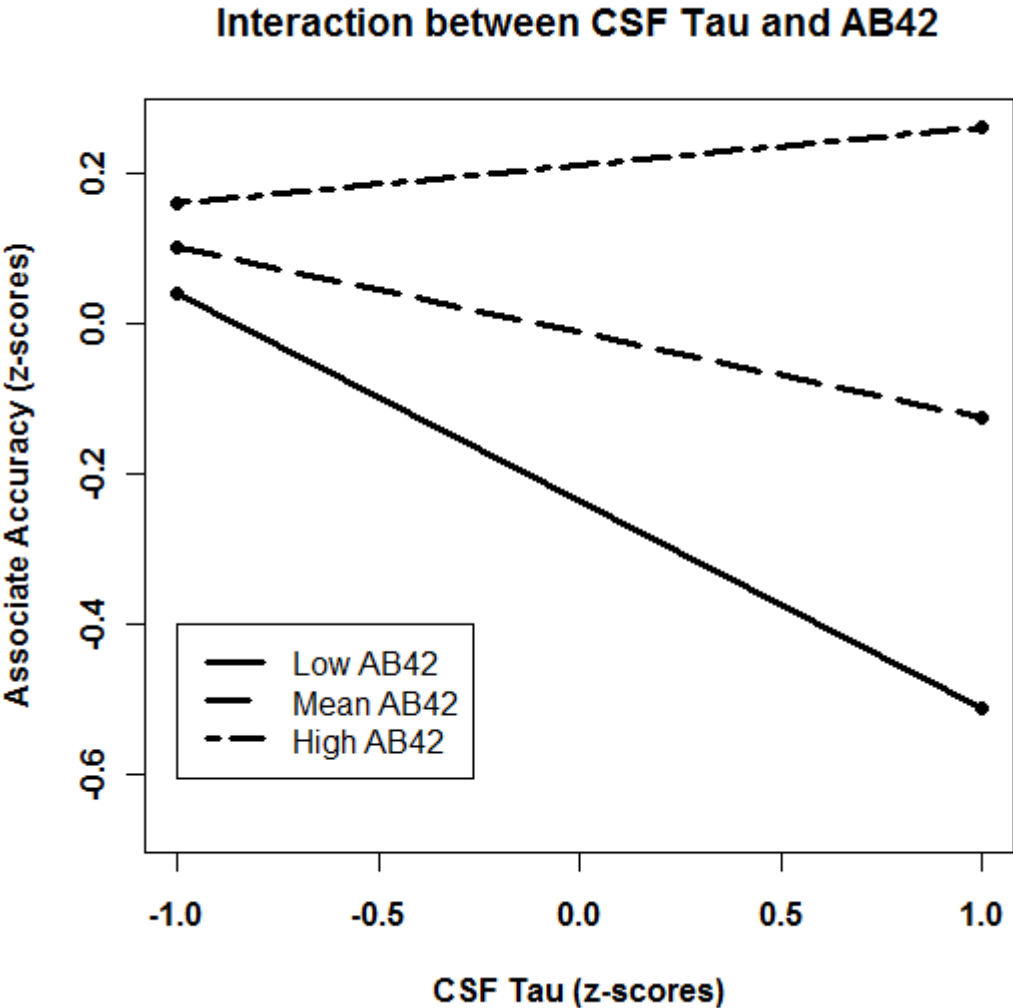
series of regression analyses predicting the level of one of the biomarkers (tau, p-tau, Aβ42, and PIB) from performance on standard psychometrics and the SVT. Similar to our previous analyses, we first partialed age, education, and assessment date, and then entered each specific psychometric test in the first step of the regression and associate accuracy from the SVT in a second step. As can be seen in Table 3, the accuracy measure significantly predicted biomarker levels above and beyond all the psychometric tests here. Furthermore, very few of the standard psychometrics showed any relationship to the biomarkers and none were consistently related to all the markers, as was the case for the associative accuracy measure.

Thus, it appears that the SVT is sensitive to the levels of biomarkers in cognitively normal controls when many standard psychometric tests are not. In this light, it is interesting that accuracy performance in this task was also able to discriminate between carriers and noncarriers of genetic mutations for autosomal dominant AD (Storandt, Balota, Aschenbrenner, & Morris, 2013). This provides converging evidence that the SVT is a sensitive measure of underlying biological changes preceding onset of AD in a particularly relevant cohort.

General Discussion

The purpose of the present research was to provide an examination of the combined influence of semantic retrieval and attentional control in discriminating healthy aging from early stage Alzheimer disease, and the sensitivity of these measures to healthy control individuals who are at varying risks of developing AD, based on well-studied biomarkers. We discuss each of these issues in turn.

SVT Performance in Healthy Aging and Early Stage AD

It is clear that very mild AD participants are impaired on explicit semantic retrieval tasks (Canning et al., 2004; Hodges et al., 1992; Kirshner et al., 1984; Marczinski & Kertesz, 2006)

Table 3. R^2 change of adding associate accuracy above and beyond psychometric tests in accounting for levels of biomarkers

Variable / Test	Tau		P-tau		Aβ42		PIB	
	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2
MMSE	.006	.016*	0	.023*	.01	.064**	.02*	.067**
Animal Fluency	.003	.017*	.007	.02*	0	.075**	0	.08**
Trail Making A	0	.02*	.005	.022*	.008	.068**	.012	.071**
Letter Number Sequencing	.007	.023*	.019*	.03*	.044**	.059**	.011	.072**
Selective Reminding	.004	.019*	.006	.022*	.001	.073**	.001	.082**

* indicates $p < .05$
** indicates $p < .01$

and on tasks which place a high demand on attentional control systems (see reviews by Balota & Faust, 2001; Faust & Balota, 2007). In the present study, we used a version of the semantic verification task that places a high demand on both explicit semantic retrieval processes and attentional control.

As expected, the accuracy to the associate foils decreased both in healthy aging and in very mild AD, suggesting a breakdown in the ability to control the strong associative information in order to produce a correct "no" response. The pattern in the RT data was more complex. While the older adults were not disproportionately slowed to the associate items, there was a trend toward a larger strength effect in the associate items. AD participants, on the other hand, were slowed to the associate items overall, but not disproportionately so to the stronger items, after general slowing was accounted for. This pattern mimics earlier findings from a Stroop paradigm by Spieler et al. (1996), Balota, et al. (2010), Hutchison, et al. (2010), and Duchek et al. (2013). In each of these studies, the accuracy measures were more sensitive to AD related changes than the response latency measures, after one controls for general slowing. The authors reasoned that AD individuals are more likely to allow inappropriate but prepotent stimulus dimensions to drive their responses rather than take additional processing time to be able to make a correct response. Similarly, the early stage AD participants in the present study may have allowed the prepotent familiarity signal from the associative information drive their response which was manifested as an increase in the error rates.

This interpretation is also supported by the analysis of quantile RTs and parameters of the diffusion model. Specifically, in the comparison of healthy aging, slowing in the tail of the weak category distribution was observed. Furthermore, this slowing was not modulated by age. In other words, young adults and older adults were equally slowed in the tails of these distributions.

We interpreted this null finding as evidence that healthy adults are able to prospectively prime specific areas of semantic memory in response to the category cue. Conversely, AD participants appear not to be engaging such a strategy as there was no difference across the quantiles of their weak distributions. Such a priming mechanism (Balota, Yap, Cortese & Watson, 2008) also explains why we observed an increase in the Mu parameter of the ex-Gaussian in AD contrary to prior research (Tse et al. 2010).

Finally, the diffusion model indicated age-related changes in SVT performance was reflected in the non-decision time, boundary separation and drift rate parameters. Interestingly, the increased distributional skewing we observed in AD was due entirely to changes in the drift rate as opposed to response boundaries. Again, we argue that this is a reflection of deficient attentional control in that an inability to inhibit the associative information from the foil items decreases the drift rate for those items. To our knowledge, this is the first diffusion model analysis of performance in AD and future research should replicate these findings in standard attentional control tasks such as Simon and the flanker tasks.

Overall, the pattern of results in the current study is quite consistent with previous research indicating very mild AD participants have pronounced difficultly overcoming highly salient and familiar information in order to make a correct response (cf. Spieler et al. 1996). In this light, it is worth noting a related study using an episodic memory paradigm. Specifically, Balota et al. (1999) investigated AD performance in the DRM paradigm, in which participants are presented with a list of words (e.g. "chill", "frost", "ice") which are all semantically related to a critical, but non presented, item (e.g. "cold), and are then given a free recall test on the presented items. The results from Balota et al. showed that AD participants have an increased tendency to falsely recall items, i.e. they are more likely to recall the critical non-presented item,

given their level of veridical recall, compared to healthy older adults (see also Watson, Balota & Sergent-Marshall, 2001).

In the DRM task, it is necessary to discriminate different sources of activation (i.e. items that were encoded at study from critical lures that are activated via association to the presented items). Balota et al. argued that breakdowns in the attentional control mechanism prevent AD participants from successfully making this discrimination and thus they exhibit high levels of false recall. Similarly, in the current SVT, AD participants are less able to distinguish between items that activated by association to the category and items that are actually members of the category, and hence incorrectly respond "yes, the target belongs to the category" when presented with an associatively related lure. The important observation here is that there appears to be a parallel in the pattern of errors across two very distinct tasks.

Sensitivity to Biomarkers in Healthy Controls

The critical finding in the present study is that the attention demanding associate condition is remarkably sensitive to the buildup of AD biomarkers in a large, well-characterized sample of non-demented control individuals. It is noteworthy that these relationships were only reliable in the associate measures and not in the measures from the category condition with the sole exception of the category Mu parameter. This pattern suggests that attentional control mechanisms in semantic memory retrieval may be a key mediator of the relationship between the biomarkers and cognition. Importantly, the accuracy in the associate condition is a particularly powerful indicator of AD risk and correlates significantly with all four biomarkers analyzed here, above and beyond many standard psychometric tests. Our analysis also showed both tau and Aβ42 account for unique variance in associate accuracy, and when abnormal levels of both are

present the effects on accuracy are further enhanced. Finally, we were able to show the effect of ApoE4 status on cognitive performance is entirely mediated through the CSF biomarkers.

Research has repeatedly demonstrated the effects of the two processes of AD, amyloid plaques and neurofibrillary tangles, are independent, yet synergistic (Delacourte et al., 2002, Storandt et al. 2012). Interestingly, the constellation of brain regions known as the default mode network (DMN) appears to be selectively vulnerable to early amyloid deposition and disruption in this network has been shown in healthy aging and AD (Andrews-Hanna et al. 2007; Sperling et al. 2009). In this light, it is worth noting that Duchek et al. (2013) have recently demonstrated Stroop accuracy performance was sensitive to resting state connectivity in the DMN in healthy control participants and this relationship was totally modulated by CSF levels of Aβ42. It is possible that the DMN is related to attentional control systems since it is often suppressed when tasks are engaged (Raichle, 2010; Raichle et al. 2001). If the DMN is not as strongly suppressed in individuals who are at risk for developing AD, it is possible that these participants are more likely to be driven by the prepotent stimulus dimensions (i.e. word dimension in Stroop or the associative information in the SVT). Specifically, as amyloid burden increases in the DMN, and task-related disengagement of this network decreases, failures to control the prepotent response (and therefore respond incorrectly) will increase. However, it is interesting that accuracy proved to be more strongly correlated with AD pathology than either the parameters of the ex-Gaussian or the diffusion model. One may have expected the diffusion model in particular to be more sensitive to disease pathology because it accounts for both accuracy and RT data. There are a few possible reasons for the lower correlations in the more subtle measures.

First, in order to adequately recover diffusion parameters, a relatively large number of trials (and particularly trials on which an error occurs) are necessary. Even though there were 80

trials per condition in the present study, there was likely a substantial amount of noise inherent to the parameter fitting which could be obscuring some of the relationships. A second possibility is that while the diffusion model permits the decomposition of summary measures such as RT and accuracy into component processes (drift rate, boundary separation etc.), it is possible that each component itself isn't correlated with pathology but rather some combination of them. For example, accuracy is influenced by both boundary separation and drift rate. Therefore, a certain combination of boundary and drift will give rise to a specific level of accuracy (and a corresponding RT distribution). Thus, how boundary separation and drift rate change in tandem may the key indicator of AD pathology rather than how they change in isolation.

However, despite not being significantly related to CSF tau and p-tau, the associate drift rate, the non-decision time, and the associate Mu parameter were all reliably correlated with Aβ42 and PET PIB, which has psychologically interpretable meaning. First consider the drift rate, which indicates that as amyloid pathology is accumulating in the CSF and in the brain, the quality of evidence entering the diffusion process decreases. We have argued that drift rate in this condition can reflect attentional control in that the associative information will cause evidence to build towards the (incorrect) category boundary. Individuals with deficient attentional control will allow more of the associative information to drive their response, which will further decrease the estimated drift rate. Thus, it appears that amyloid pathology is directly affecting this measure of attentional control. The link to the DMN can again be made here. It is possible that because of increasing amyloid burden, individuals at increased risk of AD are less able to disengage the DMN and consequently are less able to control prepotent responses when confronted with an associative foil (Duchek et al. 2013). Future research might address this implication directly by correlating drift rate with measures of DMN connectivity.

Second, we consider both the non-decision time and associate Mu parameters together as they are typically highly correlated (Matzke & Wagenmakers, 2009). The correlation with amyloid burden suggests AD pathology increases the duration of residual operations such as stimulus encoding and memory access. This is intriguing in light of the prospective priming hypothesis. Specifically, we have argued that AD individuals are unable to engage a prospective memory search in response to the category cue but instead wait for the target item. Indeed Balota et al. (2008) have provided evidence that semantic priming under standard conditions primarily influences the Mu parameter of the ex-Gaussian. This pattern is most consistent with a prospective or headstart interpretation of priming. Thus, the reason there are large Mu differences between controls and AD participants is that the former group are engaging prospective priming strategies whereas the latter are not. In this light, increasing AD pathology could be influencing an individual's ability to engage prospective processes due to the high attentional demands of such a strategy.

It is important to keep in mind that while the parameters of the diffusion model are themselves psychologically interpretable, the relationships with the biomarkers are entirely correlational. In other words, we have determined that decreased drift rates and increased non-decision time are related to amyloid burden, but the pattern of causality cannot be established in the current design. As such, future studies should seek to replicate these findings.

Conclusions

It is clear that the relationship between AD biomarkers and cognitive performance is nuanced and provides an important avenue of future research. As noted previously, investigations of the relationship between AD biomarkers and cognitive performance have yielded mixed results, with some measures showing correlations mainly with the ratio of two

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biomarkers (Nordlund et al. 2008), or no relationship at all (Fagan et al. 2009, Vemuri et al ,

2011). In this light, it is compelling that the associate measures are showing robust sensitivity to

the accumulation of isolated biomarkers as well as their interaction (in the case of accuracy).

These results add to the growing body of research implicating a key role of attentional

control mechanisms in early stage AD (Balota et al. 2010; Hutchison et al. 2010, Perry &

Hodges, 1999; Tse, Balota, Yap, Duchek & McCabe, 2010, Twamley et al., 2006). Moreover,

we have provided evidence that the combination of attentional control with a semantic retrieval

task is particularly sensitive in discriminating not only healthy controls from individuals with

very mild AD, but can also discriminate healthy control participants who are at increased risk to

develop AD based on the buildup of AD-related biomarkers. Indeed, the combination of

attentional control and semantic retrieval required by the SVT is sensitive to biomarkers which

are largely independent. Thus, we argue it is important to further explore the combination of

attentional control and memory retrieval processes in cognitive tasks to gain a better

understanding of AD-related pathology in non-demented older adults. Clearly, longitudinal

research is needed to further clarify these relationships.

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