

## Cognitive aging in persons with minimal amyloid- $\beta$ and white matter hyperintensities



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### ABSTRACT

Substantial individual differences exist in the magnitude of the cognitive decline associated with normal aging. Potential contributors to this intersubject variability include white matter hyperintensities (WMH) and preclinical Alzheimer's disease, evident as increased brain amyloid. This study examined whether older individuals with minimal evidence of WMH and/or brain amyloid-beta (seen on positron emission tomography with the Pittsburgh compound B radiotracer—PiB) still showed significant cognitive decrements compared to the young. Older individuals, conservatively screened for normal range performance on an extensive neuropsychological battery, underwent structural magnetic resonance imaging (MRI) and PiB scans and performed tests of information processing speed, working memory and inhibitory function. The elderly were divided into PiB(+) and PiB(−) groups based on radiotracer retention. There were no significant differences in cognitive performance between PiB(+) and PiB(−) elderly. However, both PiB groups performed significantly worse than did the young on cognitive testing. WMH burden in the same individuals was quantified by consensus ratings using a 10 point scale with a median split defining two groups, WMH(+) and WMH(−). There were no differences in cognitive performance between WMH(+) and WMH(−) individuals, but both WMH groups performed significantly worse than did the young. Older participants who were both PiB(−) and WMH(−) also performed significantly worse than did the young in all three cognitive domains. The present results suggest that normal-elderly individuals whose brain scans show minimal evidence of amyloid deposition or WMH, still demonstrate a major decrement in comparison to younger persons on measures of processing resources and inhibitory efficiency.

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### 1. Introduction

A large literature documents the decline in cognitive performance associated with increasing age (Rabbitt, 2002). This is commonly thought to reflect an intrinsic deterioration over time in the complex neurological systems responsible for cognition, described by Drachman (2006) as being the “biologic manifestations of increasing entropy”. However, there are substantial between-person differences in the magnitude of this age-associated cognitive impairment (Ardila, 2007). Potential sources for some of this intersubject variability have emerged from brain-imaging studies

showing structural evidence of white matter abnormalities in the form of white matter hyperintensities (WMH) in the majority of older persons, despite the absence of clinical symptoms of major cerebrovascular disease (Longstreth et al., 1996). These WMH are associated with poorer cognitive performance in putatively normal elderly persons (Gunning-Dixon & Raz, 2000; Rabbitt et al., 2007; Söderlund et al., 2006) suggesting that some of the cognitive decrements ascribed to normal aging may reflect extrinsic age-associated disease, possibly of vascular origin.

Another possible contributor to the cognitive problems found in the elderly is preclinical Alzheimer's disease (AD) (Sperling et al., 2011). The risk for AD increases with advancing age and its onset is insidious, producing a decline in cognitive functioning long before the disease can be clinically detected (Bäckman, Jones, Berger, Laukka, & Small, 2005). Thus, cognitive aging studies are

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likely to have individuals with preclinical AD within their “normal old” sample. Such persons could pull down the mean cognitive performance of the older sample leading to an overestimation of both the magnitude of the effect that aging has on cognitive performance and the degree of intersubject variability. Supporting evidence comes from a study that tested presumably normal-elderly individuals and then followed them longitudinally. When baseline data from individuals who later demented were removed from that of the total elderly sample, there was a substantial rise in the mean performance of the group as well as a decrease in between-subject variability (Holtzer et al., 2008). Thus, part of the cognitive decrement commonly attributed to normal aging may actually result from inclusion in research studies of older individuals in whom the pathophysiological changes of AD have already begun.

Development of the radiotracer Pittsburgh Compound B (PiB) allows the amount of fibrillar amyloid-beta ( $A\beta_{\text{fibr}}$ ) deposition present in the brains of living persons to be measured by positron emission tomography (Klunk et al., 2004).  $A\beta$  oligomerization and deposition is thought to play a crucial role in the development of AD (Jack et al., 2010) and thus, this radiotracer permits amyloid-related brain changes associated with AD to be detected before the disease can be clinically diagnosed. This makes it possible to examine the potential contribution of preclinical AD to the cognitive decrements usually attributed to normal aging by determining which individuals within a sample of supposedly normal-elderly carry a significant  $A\beta_{\text{fibr}}$  burden in their brains. Studies using PiB imaging have found that 25% to 35% of “normal” elderly individuals show elevated levels of  $A\beta_{\text{fibr}}$  deposition (Aizenstein et al., 2008; Oh et al., 2011; Pike et al., 2011; Storandt, Mintun, Head, & Morris, 2009). The percentage of individuals with high PiB retention increases with age (Rodrigue, Kennedy, & Park, 2009; Morris et al., 2010; Rowe et al., 2010) and is greater in those who carry one or more copies of the  $APOE\epsilon 4$  allele of  $APOE$  (Morris et al., 2010; Rowe et al., 2010; Kantarci et al., 2012), a known genetic risk factor for AD.

The various cognitive decrements seen with increasing age have been proposed to result from a reduction in either general-purpose processing resources or in the efficiency with which these resources are allocated (Rabbitt, 2002). Age-related changes in processing resources have been conceptualized both as a limitation in working-memory capacity (Park & Hedden, 2001) and as a slowing in the rate of information processing (Salthouse, 2000). A related view is that a decrease in the efficiency with which older individuals inhibit irrelevant or distracting information from entering working memory is responsible for many of the cognitive impairments associated with old age (Hasher, Tonev, Lustig, & Zacks, 2001).

There is growing evidence that WMH contribute to an impairment in these basic cognitive resources (Gunning-Dixon & Raz, 2000; Rabbitt et al., 2007; Söderlund et al., 2006). However, the effect that increased  $A\beta$  deposition in the older brain has on information processing speed, working memory and inhibitory function is not clear. While elevated PiB retention (as a marker for  $A\beta_{\text{fibr}}$  deposition) has been associated with impaired cognitive performance in persons with mild cognitive impairment and AD (Grimmer et al., 2009; Wolk et al., 2009), studies examining the relation of amyloid burden to mental performance in clinically-unimpaired elderly have either found no significant effect (Aizenstein et al., 2008; Storandt et al., 2009; Oh et al., 2011) or have shown an association of elevated PiB retention primarily with decrements in episodic memory (Perrotin, Mormino, Madison, Hayenga, & Jagust, 2012; Pike et al., 2007, 2011). However, even the relation with memory is not uniformly found (Jack et al., 2008). Most of these studies have used standardized neuropsychological measures often combined into composite scores (e.g., Oh, Madison, Haight, Markley, & Jagust, 2012) in an

attempt to determine whether PiB retention can serve as an early marker for AD prior to the onset of clinical symptoms. However, such neuropsychological measures typically require multiple complex cognitive operations rather than focusing on the basic mechanisms central to research and theory in cognitive aging. Thus, these results do not directly address whether preclinical AD contributes to the decrements in processing resources and inhibition associated with normal aging.

There are, however, two studies that have, with conflicting results, examined the relation between  $A\beta_{\text{fibr}}$  burden and measures of processing resources. Rodrigue et al. (2012) measured brain  $A\beta_{\text{fibr}}$  and cognitive performance in participants aged 30–89 and found that increased  $A\beta_{\text{fibr}}$  burden was associated with a decrease in processing speed but not working memory. When the analysis was restricted to just those individuals whose  $A\beta_{\text{fibr}}$  load exceeded the 95% confidence interval from the regression of age on PiB (all of whom were over age 60), increasing  $A\beta_{\text{fibr}}$  load was correlated with impaired processing speed, working memory and reasoning. By contrast, a study from our lab (Aizenstein et al., 2008) found clinically-unimpaired elderly who were PiB(+) (i.e., their amyloid burden fell above a specified cutoff) did not perform significantly worse than did those who were PiB(–) on measures of working memory, decision time and inhibitory efficiency. There are a number of methodological reasons why the two studies had differing results, including use of different radiotracers. However, one potentially important factor not controlled for in either study, or for that matter in any of the studies that have examined the relation between PiB retention and performance, is the presence of co-existing white matter pathology within the sample. As noted above, WMH are common in older persons and are also associated with cognitive decrements in processing speed, working memory and executive function. There is also evidence that vascular risk factors such as hypertension as well as increased WMH severity are associated with increased amyloid deposition (Grimmer et al., 2012; Rodrigue et al., 2013) and that white matter changes may have an additive effect on the cognitive decrements found with AD (Bracco et al., 2005; Brickman et al., 2008). Thus, it is important to examine whether age-related white matter abnormalities may complicate attempts to determine the relation between normal aging, amyloid burden and cognitive performance.

An additional source of data is necessary to examine the contribution of amyloid and/or WMH to the cognitive decrements associated with normal aging and that is a younger comparison sample. Such a comparison group was recently examined in a study using PiB imaging (Oh et al., 2012) which compared the effects of age and of  $A\beta_{\text{fibr}}$  deposition using a broad range of clinical neuropsychological tasks. The group differences they found on individual neuropsychological tasks were due primarily to age rather than PiB status, although when all the neuropsychological results were reduced to a global composite score they were able to demonstrate a difference between PiB(+) and PiB(–) elderly individuals.

The present study tested a group of elderly volunteers who had been administered an extensive battery of normed neuropsychological instruments and determined to be unimpaired according to clinical criteria. These individuals were then given multiple tests of information processing speed, working memory and inhibitory function and their performance compared to that of a younger sample given the same tests. The older participants also received a structural MRI scan to measure WMH severity and a positron emission tomography (PET) scan with PiB to measure brain amyloid burden. By obtaining imaging data on both amyloid and WMH burden it was possible to examine the contributions that these two major age-related neuropathologies make to cognitive decrements usually attributed to normal aging. The major question was the degree to which the pattern and severity of cognitive

decline associated with normal aging persisted after accounting for the presence of white matter abnormalities and amyloid found in the brains of persons who would qualify as normal elderly in cognitive-aging studies.

## 2. Method

### 2.1. Participants

The 71 older participants reported in this analysis ranged in age between 65 and 88 and had at least 12 years of education (see Table 1). They were recruited from the community by advertisements and direct mailings to individuals who had previously expressed an interest in participating in aging studies. Exclusion criteria included a history of major psychiatric or central nervous system disease, use of psychoactive medications (i.e., narcotics, benzodiazepines, sedatives), a score on the Geriatric Depression Scale (30 point version—Yesavage et al., 1983) greater than 15, or any contraindications for receiving an MRI. Individuals were also excluded if their performance on an extensive neuropsychological assessment battery yielded results suggesting the presence of MCI or dementia. The exclusion criteria for the present study were stricter than is typical for most studies of cognitive aging in that the participants' scores on neuropsychological testing were required to be within the range of "clinically unimpaired". Data from forty-three of the individuals in the present analysis were previously reported in the Aizenstein et al. (2008) which compared cognitive performance in PiB(+) and PiB(−) elderly but did not examine the effects of WMH or of normal aging.

Cognitive results were also available from a younger sample of 37 individuals between 18 and 30 years of age with a level of education similar to that of the old (see Table 1). These individuals had participated in an earlier study using the same cognitive measures employed with the older sample, but had not undergone neuropsychological testing or brain imaging.

### 2.2. Neuropsychological assessment


Potential older participants were given a neuropsychological screening battery used by the University of Pittsburgh Alzheimer Disease Research Center thus allowing use of consensus diagnostic criteria to identify and exclude individuals who would meet criteria for MCI (Petersen, 2004; Windblad et al., 2004; Wolk et al., 2009) or dementia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 1994). These measures broadly assessed: (a) *memory* (Word List Learning from the Consortium to Establish a Registry in Alzheimer's Disease battery, Logical Memory Story A from the Wechsler Memory Scale–Revised, modified Rey Osterrieth [R–O] figure recalls); (b) *visuospatial construction* (modified block design subtest from the Wechsler Adult Intelligence Scale–Revised [WAIS–R], copying of the R–O figure); (c) *language* (semantic and letter fluency, Boston Naming Test); (d) *attention and executive functions* (Trail Making Test A & B, Digit Symbol Substitution Test and digit spans forward and backward from the WAIS–R,

paper and the pencil version of the Stroop test, clock drawing, and abstract reasoning subtest from the Mattis Dementia Rating Scale). The results were reviewed by neuropsychologists (B.E.S., J.A.S.) from the Alzheimer center to determine whether a participant met criteria for clinical impairment and thus should be excluded. These criteria were not dictated by strict score cutoffs but were clinically guided (Petersen et al., 1999) by the following principles: (a) there was evidence on at least two different tests of performance significantly below expectations given the individual's age and educational background (scores were generally considered to be in the impaired range if they fell more than 1SD below age means taking into account the individual's level of education); (b) low test scores were supported by reports from the participant of changes or concerns about memory or cognition or by behavioral observations by study staff. Persons excluded on this basis would have met neuropsychological criteria for MCI or dementia at the University of Pittsburgh Alzheimer Disease Research Center. In addition to the 71 participants whose data are reported here, an additional 37 older individuals were excluded on the basis of their neuropsychological results.

Participants were also given the Wechsler Test of Adult Reading (Wechsler, 2001). Performance on this task is relatively resistant to the cognitive decline associated with normal aging and brain disease and thus provides an estimate of the individual's premorbid intellectual ability.

### 2.3. Cognitive assessment

#### 2.3.1. Information processing speed

There were two measures of choice response time. One required a perceptual comparison in which the participant had to decide whether two shapes (Word "Wingdings") presented side by side on a computer screen were physically identical (e.g., ). In this task, all the information necessary to make a decision was provided by the physical stimuli. Participants pressed a button with the index finger of their dominant hand if the two shapes were the same and a button with index finger of the other hand, if they were different. The second task (conceptual comparison) required participants to retrieve semantic information in order to make a decision. They saw two stimuli (single letters and digits) and had to decide whether they were from the same category (i.e., either both letters or both digits—e.g., L X or 5 9) or were from different categories (e.g., L 5). They responded the same as in the previous task. Mean response times for correct "same" trials in both tasks were used in the analyses.

As a measure of sensorimotor speed, participants were given a task in which they pressed a button with their dominant hand as soon as a one centimeter dot appeared in the center of the computer screen. The interval between the subject's response and the appearance of the next dot varied randomly between 1.5 and 3 s to reduce anticipatory responses.

#### 2.3.2. Working memory

Two different loaded-span tasks measured the amount of information participants could retain over a short time while simultaneously carrying out an attention-demanding mental operation. The first was the N-back task (Dobbs & Rule, 1989) in which they listened to a string of ten digits presented by a computer

**Table 1**

Personal characteristics and cognitive performance of older participants in the PiB positive and PiB negative groups and of a young comparison group.

	PiB(+) Elderly N=18		PiB(−) Elderly N=53		Young N=37	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age <sup>a,b</sup>	76.2	(5.9)	73.6	(5.1)	22.6	(3.3)
Education in years	14.6	(2.9)	14.8	(2.6)	14.1	(2.0)
Percent female	50%	–	71.7%	–	64.9%	–
WTAR Predicted IQ	106.6	(10.8)	107.6	(9.3)	–	–
Percent APOE *4 carriers <sup>c</sup>	37.5%	–	11.5%	–	–	–
<b>Information processing speed</b>						
Perceptual comparison RT (ms) <sup>a,b</sup>	767.6	(155.8)	756.6	(179.1)	527.1	(74.1)
Conceptual comparison RT (ms) <sup>a,b</sup>	814.5	(184.2)	758.2	(149.8)	623.8	(66.4)
Sensorimotor RT (ms) <sup>a,b</sup>	266.3	(55.2)	265.6	(44.9)	230.7	(58.6)
<b>Working memory</b>						
N Back (/60)	34.3	(12.6)	31.9	(11.7)	38.2	(12.8)
Letter–number sequence (/21) <sup>a,b</sup>	9.0	(2.7)	9.8	(2.9)	12.6	(3.0)
<b>Inhibitory control</b>						
Stroop: no. of intrusions <sup>b</sup>	3.1	(3.0)	2.8	(2.6)	1.5	(1.6)
Stroop: response-time diff. (ms) <sup>a,b</sup>	123.9	(86.4)	105.0	(65.2)	60.6	(51.0)
Hayling: No. of intrusions	5.1	(3.3)	4.3	(3.6)	3.1	(3.7)
Hayling: response-time diff. (ms)	2601.9	(2284.4)	1736.8	(1813.6)	1228.6	(2495.8)

<sup>a</sup> PiB(−) elderly were significantly different from the young.

<sup>b</sup> PiB(+) elderly were significantly different from the young.

<sup>c</sup> PiB(−) elderly were significantly different from PiB(+).



at the rate of one digit every 2 s. As they heard each digit, they were to say the digit that had occurred  $N$  back in the string where  $N$  ranged between 0 and 5. In the  $N=0$  condition they simply repeated the digit they had just heard while in the other conditions they had to repeat a digit from earlier in the list. For example, in the  $N=2$  condition if given the digit string “5, 2, 7, 8, 6...”, they would say nothing after the first two digits then, after hearing “7”, they would say “5”, after hearing “8”, they would say “2”, etc. A string was presented until the participant made an error. Participants were given two digit strings at each  $N$  with each string requiring ten responses. The score on each string was the number of correct responses a participant gave before making an error. The result used in these analyses was the sum of the participants' highest scoring string in each of the six levels of  $N$  (i.e., 0–5) for a maximum score of 60. The second working memory task was the Letter-Number Sequencing subtest adapted from the WAIS III (Psychological Corporation, 1997) in which the participant saw on the computer screen a sequence of numbers and letters (e.g., 6, M, 2, K, 3) at the rate of one item per second. After seeing all the items, they first recalled the numbers in ascending order and then the letters in alphabetic order (i.e., 2, 3, 6, K, M). The number of letters and numbers presented began at two and increased up to eight. Each difficulty level consisted of three trials with the same number of numbers and letters (although the actual letters and numbers were varied). The score on this task was the total number of trials on which the participant's response was totally correct.

### 2.3.3. Inhibitory efficiency

Two tasks assessed the efficiency with which participants could inhibit prepotent responses that were irrelevant in their current context. In a computerized version of the Stroop test (adapted from Spieler, Balota, & Faust, 1996) a stimulus word appeared on a computer monitor and the participant had to name aloud the color of the letters making up the word. The vocal response triggered a voice key stopping a timer started by presentation of the stimulus. In one condition (Incongruent), the stimuli were color names (“red”, “green”, “yellow” or “blue”) presented in an incongruent color (e.g., the word “red” spelled out with green letters). In the other (Neutral), the stimuli were four noncolor words of a similar frequency in the language (“bad”, “poor”, “deep” and “legal”) also presented in one of the four colors. Trials from the two conditions were randomly intermixed. The two measures of inhibitory efficiency were the mean response-time difference between the conditions (incongruent minus neutral), as well as the number of intrusions on the incongruent trials (defined as partial or full enunciation of an incorrect response).

The Hayling test (Burgess & Shallice, 1996) compared the time participants took to generate a one-word ending to a sentence whose semantic context was highly constraining (e.g., “He scraped the cold food from his \_\_\_\_”). For one set of sentences (part A) participants were to generate a one-word ending that made sense (e.g., “plate”) while for another set of sentences (part B) they had to generate a nonsensical ending for each sentence. Thus, part B required that the participant inhibit highly salient responses in order to produce a semantically incongruous ending. Each sentence was presented auditorially by a computer and in the place where the last word would fall there was a tone which was the signal to respond. Measures of inhibitory efficiency were mean response-time difference between the two parts of the task (B minus A), as well as the number of intrusions (partial or full enunciation of an incorrect response) made in part B.

### 2.4. MRI methodology

MRIs were collected on 68 of the 71 total participants using a 1.5 T Signa Scanner (GE Medical Systems, Milwaukee, WI) and on three participants using a 3-T Siemens Trio TIM scanner. White matter hyperintensities were assessed using T2-weighted FLAIR (3 T sequence: TR=9,160 ms, TE=90 ms [effective]; TI=2500 ms, number of excitations=1) using an interleaved acquisition (48 slices, 3-mm slice thickness, no gap) and on the 1.5 T machine (TR=9004 ms, TE=172.5 ms [effective]; TI=2200 ms, number of excitations=1) using an interleaved acquisition (24 slices, 4-mm slice thickness, a gap of 1 mm). While all participants received an MRI, two persons requested to be removed from the scanner before the FLAIR sequences could be completed, while FLAIRS from another three individuals were technologically inadequate. Thus, WMH results were available for 66 individuals.

Three raters (WEK, HJA, ADC) evaluated WMH on the FLAIR images using a numerical rating system (Cardiovascular Health Study—Yue et al., 1997) with predefined visual standards representative of progressive severity within a 10-point scale (0 through 9). The three raters simultaneously viewed and discussed the scoring until a consensus score was reached taking into account differences in field strength. In no cases did the pre-consensus scores differ by more than one point. Low WMH was defined as scores of 0–2 and high WMH was defined as 3–9.

### 2.5. PET methodology

[<sup>11</sup>C]PiB was produced and PiB-PET data were collected and analyzed as previously described (Price et al., 2005). The individual participant's MRI was utilized for co-registration and region of interest definition (Price et al., 2005; Cohen et al., 2009) and for correcting PiB-PET data for the diluting effects of

expanding cerebrospinal spaces accompanying cerebral atrophy (Meltzer et al., 1999). PiB was injected intravenously (12–15 mCi, over 20 s, specific activity ~1–2 Ci/μmol) and PET scanning was performed over 90 min. Analysis of the PiB PET data utilized a standardized uptake value ratio (SUVR) 50–70 min post-injection. To determine SUVR, SUV was determined by normalizing regional tissue radioactivity concentration to injected dose and body mass and each regional SUV was divided by the cerebellar reference SUV that was representative of free and nonspecific radiotracer retention. Thus, the final SUVR is equivalent to a tissue ratio.

The PiB PET data were acquired within six weeks of clinical screening and cognitive testing. Cutoffs for PiB-positivity were determined using the first 62 consecutive cognitively normal controls studied with PiB PET in Pittsburgh using sparse  $k$ -means clustering (SKM) with re-sampling as described previously (Cohen et al., 2013). From SKM regional cutoffs were obtained for brain regions that most commonly show amyloid deposition in AD: anterior cingulate (cutoff=1.78), anterior-ventral striatum (cutoff=1.48), frontal cortex (cutoff=1.71), lateral temporal cortex (cutoff=1.50), parietal cortex (cutoff=1.63), and precuneus cortex (cutoff=1.73). Any subject who had PiB retention values exceeding this cutoff point in any one (or more) of these six brain regions was defined as PiB(+).

### 2.6. APOE genotyping

DNA was isolated from blood using the QIAmp Blood DNA Maxi Kit protocol (Qiagen, Valencia, CA). Genotypes for two APOE SNPs, rs429358 ( $E\epsilon 4$ ) and rs7412 ( $E\epsilon 2$ ) were determined using TaqMan SNP genotyping assays (Applied Biosystems, Foster City, California).

### 2.7. Statistical analysis

ANOVA was used to compare groups on cognitive test performance, and Tukey's HSD for post-hoc pair-wise comparisons on measures for which the omnibus ANOVA was significant at  $p < .05$ . Analyses were performed without covariates. Two primary series of ANOVA models were run: (1) with PiB status as the independent variable, and (2) with WMH status as the independent variable. A secondary series of ANOVA models included both PiB and WMH status as independent variables, plus their interaction. These latter models were exploratory, as our sample size limited power for observing significant interactions. Effect sizes (Cohen's  $d$ ) reflecting the magnitude of group contrasts in cognitive performance were calculated as the difference between two group means divided by their pooled standard deviation (Lipsey & Wilson, 2001). Cohen's  $d$  was calculated for 3 pairwise group contrasts: (a) PiB(–) vs. PiB(+); (b) WMH(–) vs. WMH(+); and (c) PiB(–)/WMH(–) vs. young participants. Effect sizes were scaled so that higher  $d$ 's reflect better mean performance in pathology-negative vs. pathology-positive groups, and better performance in young vs. old.

## 3. Results

The percentage of PiB(+) elderly in the present study (25%) is similar to that of earlier studies examining the relation between PiB load and cognition in the elderly: Storandt et al. (2009)=22%; Oh et al. (2011)=36%; Pike et al. (2011)=33%; Perrotin et al. (2012)=28%. Thirty-nine percent of individuals in this study had a WMH rating of 3 or greater and thus were classified as WMH(+). In comparison, in a large community study using the same MRI rating scale (Yue et al., 1997) of those persons within the age range of individuals in this study, approximately 30% received ratings of 3 or above. Thus, despite the strictness of the neuropsychological exclusion criteria, the percentage of individuals in this study who were PiB(+) or were WMH(+) is similar to that found in previous studies of community-dwelling elderly.

There were no significant differences among PiB(+), PiB(–) elderly and the young on distribution of sex ( $\chi^2=2.83$ ,  $p=.24$ ) or on mean education [ $F(2,105)=0.79$ ,  $p=.45$ ] (see Table 1). Between PiB(+) and PiB(–), there were no differences in age [ $F(1,69)=3.08$ ,  $p=.08$ ] or estimated premorbid intellectual functioning based on Wechsler Test of Adult Reading [ $F(1,69)=0.14$ ,  $p=.71$ ], although, as expected, the frequency of APOE $\epsilon 4$  allele carriers was higher among the PiB+ individuals ( $\chi^2=5.67$ ,  $p=.02$ ).

In unadjusted ANOVA models with group as the independent variable, there were significant differences among PiB(+), PiB(–) and the young on the following cognitive measures: perceptual comparison [ $F(2,105)=30.28$ ,  $p<.001$ ]; conceptual comparison [ $F(2,105)=16.02$ ,  $p<.002$ ]; sensorimotor processing speed

[ $F(2,105)=5.59, p < .01$ ]; letter-number sequence [ $F(2,105)=13.39, p < .001$ ]; Stroop intrusions [ $F(2,104)=3.87, p=.02$ ]; and Stroop RT difference [ $F(2,104)=7.21, p < .01$ ]. There were no omnibus ANOVA differences on N-back [ $F(2,105)=2.90, p=.06$ ], Hayling intrusions [ $F(2,104)=2.15, p=.12$ ] or Hayling RT difference [ $F(2,105)=2.59, p=.09$ ]. On post-hoc pair-wise comparisons, there were no significant differences between the two PiB groupings on any of the cognitive measures (Table 1). By contrast, both PiB groups performed significantly worse than did the young on almost all of the cognitive measures. For Stroop intrusions, only the PiB+ performed significantly worse than the young.

There were no significant differences among WMH(+), WMH(−) and the young on the distribution of sex (chi-square=0.002,  $p=.99$ ) or mean education [ $F(2,100)=0.58, p=.56$ ]. Between WMH(+) and WMH(−) groups, there were no differences on age [ $F(1,64)=0.98, p=.33$ ], estimated premorbid IQ [ $F(1,64)=0.01, p=.93$ ], or percent APOE\*4 allele carriers [chi-square=0.23,  $p=.63$ ].

In unadjusted ANOVA models with group as the independent variable, there were significant differences among WMH(+), WMH(−) and the young on the following cognitive measures: perceptual comparison [ $F(2,100)=20.62, p < .001$ ]; conceptual comparison [ $F(2,100)=14.07, p < .001$ ]; sensorimotor processing speed [ $F(2,100)=5.35, p < .01$ ]; letter-number sequence [ $F(2,100)=11.85, p < .001$ ]; Stroop intrusions [ $F(2,99)=4.77, p=.01$ ]; Stroop RT difference [ $F(2,99)=8.27, p < .001$ ]; and Hayling intrusion [ $F(2,100)=3.52, p=.03$ ].

On post-hoc pair-wise comparisons, there were no differences on any of the cognitive measures between those individuals rated as WMH(+) and those rated WMH(−). In comparison to the young, both WMH groupings performed significantly worse on the measures of decision time, on Letter-Number Sequencing and on Stroop response-time difference. Only the WMH(+) individuals were significantly worse than the young on the Stroop intrusions and Hayling intrusions. As with the PiB results, comparisons between the elderly groups and the young that did not reach significance were in the expected direction (Table 2).

We determined the number of older individuals who fell into the various combinations of PiB and WMH status. Ten persons were PiB(+) but WMH(−), 19 were PiB(−) but WMH(+), and 7 were both PiB(+) and WMH(+). Thus, only 30 out of 66 individuals were free of both types of neuropathology (WMH results were missing from

5 persons and thus they could not be assigned to a group on the basis of their WMH rating). When we compared the cognitive performance of just those older participants who were both PiB(−) and WMH(−) to that of the young (results not shown), again the older subjects performed significantly worse than the young on the two decision-time tasks, the Letter-Number Sequencing task and the Stroop response-time difference measure. Results in the other measures were in the expected direction (old worse than young) but were not significant.

In a separate series of ANOVA models with PiB status and WMH status entered simultaneously as main effects and their interaction included, none of the interaction terms were significant for the cognitive measures. Of note, however, for sensorimotor RT, the PiB × WMH status interaction was near significant ( $p=.06$ ). Inspection of means revealed larger mean difference between WMH(−) and WMH(+) within the PiB(+) group (247.8 vs. 292.5 ms), compared to PiB(−) (267.2 vs. 260.9 ms).

Effect sizes (Cohen's  $d$ ) quantifying the magnitude of differences between mean cognitive scores are presented in Table 3. Overall patterns of  $d$ 's reveal that for processing speed and working memory measures, the effects of age are far greater than the respective effects of amyloid and WMH pathologies among the elderly. This pattern is less apparent for measures of inhibitory control, where most effects of brain pathologies are comparable to, or larger than, those of age alone.

Finally, Supplemental Tables 1 and 2 present mean scores on the clinical neuropsychological tests according to PiB and WMH status, respectively, showing an overall pattern of similar test performance for both groupings.

#### 4. Discussion

The primary question in the present analysis is the extent to which the cognitive decline associated with increasing age is driven by undiagnosed neuropathology. Does a significant amount of age-associated cognitive decrement remain after accounting for neuroimaging evidence of white matter abnormalities and amyloid burden? Within this healthy sample, even those older participants with little or no amyloid deposition [i.e., PiB(−)] performed significantly worse than did the young on measures

**Table 2**

Personal characteristics and cognitive performance of older participants in the WMH positive and WMH negative groups and of a young comparison group.

	WMH(+) elderly $N=26$		WMH(−) elderly $N=40$		Young $N=37$	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age <sup>a,b</sup>	75.1	(5.8)	73.8	(5.3)	22.6	(3.3)
Education in years	14.5	(2.7)	14.7	(2.6)	14.1	(2.0)
Percent female	65.4%	–	65.0%	–	64.9%	–
WTAR Predicted IQ	107.6	(10.1)	107.8	(9.6)	–	–
Percent APOE*4 carriers	20.0%	–	15.4%	–	–	–
<b>Information processing speed</b>						
Perceptual comparison RT (ms) <sup>a,b</sup>	767.4	(190.8)	761.1	(170.3)	527.1	(74.1)
Conceptual comparison RT (ms) <sup>a,b</sup>	780.1	(202.8)	770.6	(136.7)	623.8	(66.4)
Sensorimotor RT (ms) <sup>a,b</sup>	269.4	(45.6)	262.4	(49.1)	230.7	(58.6)
<b>Working memory</b>						
N Back (/60)	32.6	(12.7)	32.2	(12.0)	38.2	(12.8)
Letter–number sequence (/21) <sup>a,b</sup>	9.5	(2.9)	9.8	(2.8)	12.6	(3.0)
<b>Inhibitory control</b>						
Stroop: No. of intrusions <sup>b</sup>	3.3	(3.1)	2.4	(2.3)	1.5	(1.6)
Stroop: response-time diff. (ms) <sup>a,b</sup>	100.9	(59.3)	118.7	(75.1)	60.6	(51.0)
Hayling: No. of intrusions <sup>b</sup>	5.6	(4.4)	3.9	(3.0)	3.1	(3.7)
Hayling: response-time diff. (ms)	2517.9	(2091.9)	1668.0	(1880.9)	1228.6	(2495.8)

<sup>a</sup> WMH-negative elderly were significantly different from the young.

<sup>b</sup> WMH-positive elderly were significantly different from the young.

**Table 3**

Effect sizes (Cohen's *d*) reflecting cognitive performance differences between elderly pathology status groups and pathology-free age groups.

	PiB(–) vs. PiB(+)	WMH(–) vs. WMH(+)	young vs. PiB (–)/WMH(–)
<b>Information processing speed</b>			
Perceptual comparison RT (ms)	0.06	0.04	1.76
Conceptual comparison RT (ms)	0.36	0.06	1.45
Sensorimotor time RT (ms)	0.01	0.15	0.68
<b>Working memory</b>			
N Back	–0.2	–0.03	0.52
Letter–number sequence	0.28	0.11	0.85
<b>Inhibitory control</b>			
Stroop: No. of intrusions	0.11	0.35	0.4
Stroop: RT difference (ms)	0.27	–0.26	0.92
Hayling: No. of intrusions	0.23	0.48	0.12
Hayling: RT difference (ms)	0.45	0.44	0.07

Note: Higher Cohen's *d* reflects better mean performance in pathology-negative compared to pathology-positive groups, and in young compared to pathology-free elderly.

of information processing speed, working memory and inhibitory function. Thus, a substantial effect of age on cognitive performance remained even among individuals with minimal amyloid deposition. There was also no evidence that persons who were PiB(+), and therefore had elevated levels of brain amyloid, performed more poorly than did those who were PiB(–). Similarly, individuals in this sample with minimal imaging evidence of white matter abnormalities [i.e., WMH(–)] performed significantly worse than did a younger sample on tasks examining basic mental operations thought to be central to cognitive aging. There was also no evidence that persons with elevated amounts of WMH performed worse than did persons with low amounts of WMH on the cognitive measures. Comparing the cognitive performance of 30 elderly with no evidence of either elevated PiB or WMH burden to that of the young still yielded the typical aging effect for information processing speed, and for one of two tests of working memory and one of two measures of inhibitory function. Despite having removed persons with imaging evidence of white matter abnormalities and AD, the remaining elderly individuals still performed significantly worse than did a young sample on measures of processing resources and inhibitory function.

With respect to the effect of amyloid burden on processing speed and working memory, our results were not consistent with [Rodrigue et al. \(2012\)](#) who showed an increased amyloid load to be associated with decreased processing speed and working memory across a substantial age range. However, there are a number of methodological differences that complicate any direct comparison of the findings of the two studies, including use of continuous measures of  $A\beta_{PiB}$  values vs. classifying individuals as PiB(+) or PiB(–), differences in the range of participant ages and differences in the tracers employed (florbetapir vs. PiB). Our results are, however, consistent with work by [Driscoll et al. \(2006\)](#) who showed that those older persons who were clinically normal before death but at autopsy had neuropathological evidence of AD did not experience any greater cognitive decline prior to death than did elderly without neuropathological signs of AD. The present results are also similar to those of [Oh et al. \(2012\)](#) in that both studies found an effect of age on cognitive performance that was independent

of amyloid burden as determined by PiB load. Oh et al. did, however, show a performance difference between PiB(+) and PiB(–) elderly but only when they used a composite score combining a wide range of clinical neuropsychological measures.

Given the large number of elderly individuals in the present study excluded for clinically significant neuropsychological dysfunction, our results are not necessarily representative of the cognitive performance associated with elevated PiB retention in a less extensively screened group of community dwelling elderly, nor do they mean that an elevated amyloid burden has no effect on cognition, as there is substantial evidence that increased amyloid deposition is associated with major cognitive decrements in those persons who carry a clinical diagnosis of MCI or AD ([Grimmer et al., 2009](#); [Wolk et al., 2009](#)). Instead, the present results suggest that in a sample of elderly without evidence of clinically significant neuropsychological impairment, the influence of substantial levels of amyloid retention on cognition is minimal and is certainly dwarfed by the effect of age.

The lack of an effect of WMH on cognitive performance in our older sample differs from the substantial literature showing that WMH are associated with a variety of cognitive decrements in the elderly and especially a slowing in information processing speed ([Gunning-Dixon & Raz, 2000](#); [Rabbitt et al., 2007](#)). However, most of these studies had broader neuropsychological inclusion criteria (e.g., the cutoff for accepting older participants in [Söderlund Söderlund et al. \(2006\)](#) was an MMSE of 24 or more) and thus, their sample could potentially contain individuals with preclinical dementia.

Most cognitive-aging studies also do not report any criteria for excluding potentially cognitively-impaired individuals, or just use the MiniMental State Exam ([Folstein, Folstein, & McHugh, 1975](#)), excluding persons scoring less than 24 of 30 points (e.g., [Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010](#)) or, with a more strict cutoff, those scoring less than 26 (e.g., [Albinet, Boucard, Bouquet, & Audiffren, 2012](#)). We therefore examined the MMSE results for those individuals excluded from the present study because they did not meet neuropsychological criteria for being clinically unimpaired. Of 37 excluded individuals, 33 had MMSE scores  $\geq 24$ , while 28 had MMSE scores  $\geq 26$  and 15 scored 28 or higher. Thus, had we used inclusion criteria similar to those employed by these studies we would have included among our “normal” elderly, persons who show clinically significant neuropsychological deficits. This is in agreement with [Holtzer et al. \(2008\)](#) who found evidence for individuals with preclinical neuropathology (i.e., persons who later demented) being included within samples of old individuals assumed to be normal, thus complicating attempts to determine the effects of aging per se on cognition.

There are a number of limitations to these findings, including the possibility that diseases and conditions not assessed by this study could have contributed to the performance differences between the young and older participants. Cerebrovascular risk factors (especially hypertension) are common in the elderly and have been linked to diminished cognitive performance ([Elias et al., 2004](#); [Kuo et al., 2004](#)). While such vascular conditions as hypertension are associated with WMH severity, they are also linked to other structural brain changes including a decreased volume of gray matter ([Knopman et al., 2011](#)). Such atrophy is particularly evident in the hippocampus and frontal cortex of older adults ([Raz et al., 2005](#)), and is associated with cognitive impairments ([Taki et al., 2011](#)). There are also other less obvious age-related structural and neurophysiological alterations associated with hypertension such as changes in cerebral blood flow and metabolism and increased permeability of the blood-brain barrier ([Waldstein & Katzel, 2000](#)) which may also affect cognition. Vascular disease was relatively common in the present sample with 48% of the elderly taking medications prescribed



for hypertension or heart disease. For WMH (+) group the percentage of users was 50%, while for WMH (–) it was 45%; for PiB(+) group it was 61% while for PiB(–) was 45%. These group differences were, however, not significant.

There are also potential limitations in our imaging methods. Pathological changes in the white matter may occur well before the appearance of WMH (De Groot et al., 2013), although it is not clear that such early white matter changes impair cognitive performance. Similarly, the PiB radiotracer only detects fibrillar amyloid-beta deposits above a certain threshold and thus, sub-threshold amounts of fibrillar amyloid-beta or nonfibrillar accumulations of amyloid-beta may be present in some of the elderly subjects classified as PiB(–) in the present study and might affect cognitive performance (Fagan et al., 2009). Finally, the use of regional rather than a global cutoff for PiB-positivity could explain the absence of significant cognitive effects in the PiB(+) group since this group might contain individuals with very focal PiB deposition that would not be clinically meaningful. However, when we dichotomized PiB(+) and PiB(–) using a global cutoff, the results remained essentially unchanged.

Finally, the power of this study to detect small to medium effects is limited. For instance, the study is powered at 80% to detect mean differences between PiB(+) and PiB(–) of 0.78SD, and differences between WMH status groups for 0.72SD. In other words, the study is powered to detect large effects only for the pathology-plus groups compared to pathology-negative or the young. The power is improved for pathology-negative vs. young (80% power for 0.60SD). These power limitations are certainly an important context for interpretation of the pattern of significant results, including the lack of association between processing speed and WMH.

In summary, the purpose of the present study was to determine whether substantial age-related differences in information processing speed, working memory and inhibitory function persist after accounting for two neuropathologies commonly found in community-dwelling elderly individuals. The results suggest that even after screening out persons whose brains show imaging evidence of substantial amyloid deposition and/or WMH burden, the remaining elderly still demonstrate a major decrement in performance in comparison to a group of younger persons on measures of processing resources and inhibitory efficiency.

## Disclosure

GE Healthcare holds a license agreement with the University of Pittsburgh based on the technology described in this manuscript. Drs. Klunk and Mathis are co-inventors of PiB and, as such, have a financial interest in this license agreement. GE Healthcare provided no grant support for this study and had no role in study design, interpretation of results or preparation of this manuscript. All other authors have no conflicts of interest with this work and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2013.07.017>.

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