Meta-analysis of amyloid-cognition relations in cognitively normal older adults

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ABSTRACT

Objective: We conducted a meta-analysis of relationships between amyloid burden and cognition in cognitively normal, older adult humans.

Methods: Methods of assessing amyloid burden included were CSF or plasma assays, histopathology, and PET ligands. Cognitive domains examined were episodic memory, executive function, working memory, processing speed, visuospatial function, semantic memory, and global cognition. Sixty-four studies representing 7,140 subjects met selection criteria, with 3,495 subjects from 34 studies representing independent cohorts. Weighted effect sizes were obtained for each study. Primary analyses were conducted limiting to independent cohort studies using only the most common assessment method (Pittsburgh compound B). Exploratory analyses included all assessment methods.

Results: Episodic memory ($r = 0.12$) had a significant relationship to amyloid burden. Executive function and global cognition did not have significant relationships to amyloid in the primary analysis of Pittsburgh compound B ($r = 0.05$ and $r = 0.08$, respectively), but did when including all assessment methods ($r = 0.08$ and $r = 0.09$, respectively). The domains of working memory, processing speed, visuospatial function, and semantic memory did not have significant relationships to amyloid. Differences in the method of amyloid assessment, study design (longitudinal vs cross-sectional), or inclusion of control variables (age, etc.) had little influence.

Conclusions: Based on this meta-analytic survey of the literature, increased amyloid burden has small but nontrivial associations with specific domains of cognitive performance in individuals who are currently cognitively normal. These associations may be useful for identifying preclinical Alzheimer disease or developing clinical outcome measures. *Neurology*® 2013;80:1341–1348

GLOSSARY

AD = Alzheimer disease; **PiB** = Pittsburgh compound B.

The observation of fibrillar amyloid plaques among many cognitively normal, older adults may have several explanations: 1) amyloid plaques may not directly represent the pathophysiologic processes associated with Alzheimer disease (AD), which may include tauopathy,[1,2] 2) certain individuals may possess protective factors, or 3) such individuals may be in a preclinical phase of AD destined to eventually develop cognitive symptoms.[3–5] To evaluate these possibilities, researchers have attempted to detect subtle cognitive differences between cognitively normal individuals with and without amyloid biomarkers[6–10]; however, the empirical data remain equivocal.

There are wide differences in biomarkers of amyloid used, including histopathologic examination, assays for monomers of amyloid-β in CSF or blood plasma, and PET imaging of radioligands that bind to fibrillar amyloid plaques. Variability in the measurement of cognition is also large, ranging from tests developed for clinical use to experimental tests that may detect preclinical deficits.[11–14] Additionally, many studies have collapsed data across diagnostic groups, conflating diagnosis and cognitive status.

Supplemental data at www.neurology.org

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A key question regarding the relation between amyloid and cognition is whether cognitively normal individuals with elevated amyloid burden experience current decrements in cognition not meeting clinical thresholds, or subsequent cognitive declines eventually leading to a clinical diagnosis of AD. A second question is whether a specific profile of cognitive deficits could indicate that an individual might benefit from further assessment for preclinical AD using a biomarker. To examine these possibilities, we conducted a meta-analysis on assessment of amyloid-cognition relations exclusively in cognitively normal individuals.

METHODS

Selection criteria and search strategy. The selection criteria were that a study: 1) reported associations between amyloid (measured via CSF or plasma, imaging, or postmortem) and cognition, 2) reported results for 1 or more separable cognitive domains (i.e, not just global cognitive status), 3) had available results including only cognitively normal older adults, and 4) provided sufficient information in the publication or via contact with the authors to allow computation of effect sizes. The selection process included 3 stages: 1) an initial search stage used PubMed to identify studies to be screened for relevance via abstracts, followed by full-text screening for relevant or inconclusive abstracts, 2) a secondary screening of abstracts and full text of articles cited by identified studies or reviews,[7–10,15–18] and 3) personal communications with authors for relevant studies containing insufficient information for effect size computation; communications included requests for additional relevant studies, which were screened as above. The search period occurred through November 19, 2012 (further details in e-Methods on the *Neurology*® Web site at www.neurology.org).

Studies using comparisons between discrete groups (e.g., amyloid-positive vs amyloid-negative) and treating amyloid burden as a continuous measure were included; continuous analyses were preferred if provided. Patient-focused studies providing sufficient information on a cognitively normal control group were included. If a cognitively normal control group was indicated, but not reported separately, requests to authors were made for subgroup analyses.

Sixty-four studies representing 7,140 subjects across all domains and contributing 77 analytic datasets (table e-1) were selected for inclusion (some studies included multiple samples, multiple biomarkers, or both cross-sectional and longitudinal analyses). Because multiple publications from each research group report data from the same subjects, an independent subset of subjects (maximum of 3,495 for any domain) from 34 datasets was selected to uniquely represent each cohort (table 1). The largest sample from each cohort in each cognitive domain was selected, with more recent samples preferred for similar sample sizes. To maximize methodologic homogeneity, the primary analyses examined 16 datasets (maximum of 1,278 subjects) with independent cohorts using Pittsburgh compound B (PiB). Secondary analyses included independent cohorts across all amyloid assessment methods. Exploratory analyses of the full dataset are provided in the e-Results to estimate the potential range of results if more power is available, but caution is urged in interpreting results from these nonunique datasets.

Amyloid assessment. Amyloid assessment methods included histopathologic examination using staining and immunohistochemistry, CSF and plasma assays of amyloid-β40 and amyloid-β42 monomers, and PET imaging using PiB, florbetapir, and florbetaben (see e-Methods).

Neuropsychological assessment. The primary cognitive domains examined were episodic memory (including both verbal and spatial assessments), executive function (a broad category including tasks involving directed attention, inhibition, phonemic fluency, task-switching, and working memory), processing speed, visuospatial function, and semantic memory (including vocabulary and language tests). We also examined working memory as the only executive function subdomain reported in sufficient studies to allow separate examination. We examined global cognitive function to assess whether specific domains were more sensitive than global measures. Tasks classified to each domain are listed in the e-Methods. If a study included both a composite score and individual tasks for a domain, the composite score was used. For studies with multiple individual measures of a domain, the average effect size across measures was used.

Effect size computation and statistical analysis. Effect sizes were computed using mean differences, analysis of variance, *t* tests, or odds ratios comparing amyloid-negative and amyloid-positive groups (Cohen *d*), and from correlations or regressions treating amyloid as a continuous measure (*r*). Greater impairment associated with increasing amyloid burden was coded as a positive effect. All effect sizes were translated into *r* values, *z*-transformed, and weighted using inverse variance weighting computed from the sample size (for *r*, $w = n - 3$). Mean effect sizes were transformed back into standard *r* values for reporting purposes. Dummy-coded covariates were used to identify a single representative study from each cohort, and to account for study design (cross-sectional vs longitudinal), method of amyloid assessment, and whether age (and other nuisance variables) was controlled in the reported analysis. All results are reported using a random-effects model. Analyses were conducted using SPSS version 20.0 software (IBM SPSS, Armonk, NY) and associated macros.[19,20] Homogeneity was examined using Cochran *Q*.

In analyses combining across assessment methods, we assumed that all assessments of amyloid burden should have a similar relationship to cognition. To ensure that this does not obscure results evident with a more homogeneous methodology, we examined homogeneity across assessment methods using weighted 1-way analysis of variance and computed effect sizes separately for PET imaging with PiB, the most common assessment method.

For each statistical analysis, 7 tests were performed, corresponding to the 7 cognitive domains. We applied the Benjamini-Hochberg procedure to obtain a false discovery rate–corrected threshold using $\alpha = 0.05$ for each analysis.[21]

RESULTS

Results in PiB studies only. Although no studies were removed because of inhomogeneity (see figure 1 and e-Results), we began by examining the largest and most methodologically homogeneous subset of studies, those using PiB imaging. Sixteen of the 34 studies (47%) among the independent cohorts used PiB imaging, representing a maximum of 1,278 subjects (table 2, left). Within this subset, no domain exhibited significant inhomogeneity (all *p* values >0.35). Only episodic memory exhibited a significant effect size (table 2, left; figure e-1), and this effect was significantly larger than all other domains (all *p* values <0.05, 1-tailed)

Table 1 Study characteristics and effect sizes[a]

Author	Year	Cohort	Method	C/L	Controlled	n	EM	EF	WM	PS	VS	SM	GF
Balasubramanian	2012	90 + AS	Pathology	C	0	49	**0.02**						**0.10**
Schott	2010	ADNI	Aβ42	C	0	105	0.03	0.29		**0.13**		**0.04**	−0.09
Ewers[b]	2011	ADNI	PiB; Aβ42	L	0	124	**0.01**						**0.11**
Vemuri	2011	ADNI	Aβ42	C	1	109	0.04	**0.11**					0.00
Pike	2011	AIBL	PiB	C	0	177	**0.19**	**0.03**			**0.10**	**−0.01**	**0.08**
Lim[46]	2012	AIBL	PiB	C	0	141	0.14	0.07	**0.08**	**0.00**			0.01
Tolboom	*2009*	AMSTR	PiB	C	0	15	**0.03**	**−0.05**	**−0.05**	**−0.07**		**−0.29**	**−0.06**
Sperling	2012	AV45	Florbetapir	C	1	78	**0.27**			**0.10**		**0.01**	**0.22**
Mormino	2011	BAC	PiB	C	1	44	0.19						**0.08**
Oh[47]	2012	BAC	PiB	C	0	52	0.06	−0.02	−0.03	**−0.01**		0.21	
Oh[48]	*2012*	BAC	PiB	C	1	52	**0.13**	**0.00**	**0.03**			**−0.11**	
Driscoll	2006	BLSA	Pathology	L	0	39	−0.16	−0.04				**0.03**	
Resnick	2010	BLSA	PiB	L	0	51	**0.29**	**0.34**					**0.45**
Stomrud	2010	CMRU	Aβ42	C	0	37	**0.30**			**0.49**			**0.15**
Rodrigue[c]	*2012*	DLBS	Florbetapir	C	1	88	**0.01**	**0.16**	**0.16**	**0.31**		**−0.02**	**0.05**
Hulette	1998	DUKE	Pathology	C	0	12	**0.11**	**0.00**		**0.30**		**0.28**	**0.15**
Barthel	2011	EUR	Florbetaben	C	0	69	**0.03**						**0.03**
Fuld	1987	FULD	Pathology	C	0	9	**1.19**						
Rolstad	2011	GOTH	Aβ42	C	1	60		**0.28**	**0.28**			**0.39**	
Mielke[d]	2012	MCSA	PiB	C	0	483	**0.08**	**0.08**			**0.04**	**0.08**	**0.10**
Hedden	2009	MGH1	PiB	C	1	38	0.10	−0.15	**−0.06**	−0.05			
Hedden[11]	*2012*	MGH1	PiB	C	1	49	**−0.21**	**−0.10**		**−0.05**			
Rentz	*2010*	MGH2	PiB	C	0	66	**0.18**	−0.18	**−0.15**	**−0.11**	0.23	0.06	0.00
Gomperts[e]	*2012*	MGH2	PiB	C	1	84	0.06	**−0.13**			**−0.12**	**−0.04**	**−0.11**
Hedden[12]	*2012*	MGH-HAB	PiB	C	1	109	**0.18**	**0.00**	**0.06**	**0.03**			**0.11**
Okereke	2009	NHS	Aβ40/42	C	1	481	**0.06**						**0.09**
Aizenstein	2008	PITT	PiB	C	0	38	**−0.25**	**0.08**	**0.01**	**0.04**		**−0.01**	**−0.12**
Bennett	2012	ROS/MAP	Pathology	C	1	296	**0.11**	**0.12**	**0.12**	**0.00**	**0.01**	**−0.01**	**0.12**
Riley	2011	UK-ADC	Pathology	L	1	116	**0.16**			**0.09**	**0.22**	**0.19**	**0.16**
Li	2007	UWA	Aβ42	C	0	72	**0.00**	**0.08**				**0.24**	**0.00**
Cosentino	2010	WHICAP	Aβ40	L	1	478	0.07				**0.04**	**0.01**	**0.07**
Gu[f]	2012	WHICAP	Aβ40/42	C	0	813	**0.05**						
Storandt	2009	WU-ADRC	PiB	C	0	135	0.09	−0.03	**−0.03**		**−0.02**		**0.05**
Storandt	2012	WU-ADRC	PiB	C	1	220	**0.18**	**0.06**		**−0.01**		**0.08**	

Abbreviations: Aβ = amyloid-β; C = cross-sectional; EF = executive function; EM = episodic memory; GF = global function; L = longitudinal; PiB = Pittsburgh compound B; PS = processing speed; SM = semantic memory; VS = visuospatial function; WM = working memory.

[a] Studies are grouped by cohort, with each cohort given a unique abbreviation. Studies listed more than once contributed multiple datasets to the analysis. Effect sizes are Fisher *z* transform of *r*. The weight *w* for each study is n − 3. Boldface values were selected to represent the cohort in the independent cohorts analysis. Italicized studies indicate that effect sizes were computed in part from additional unpublished information provided by the authors. Citations are provided only for studies requiring disambiguation; complete citations for included studies are listed in the e-References.

[b] Ewers et al., 2011,[49] used imputed PiB values estimated from CSF Aβ42.

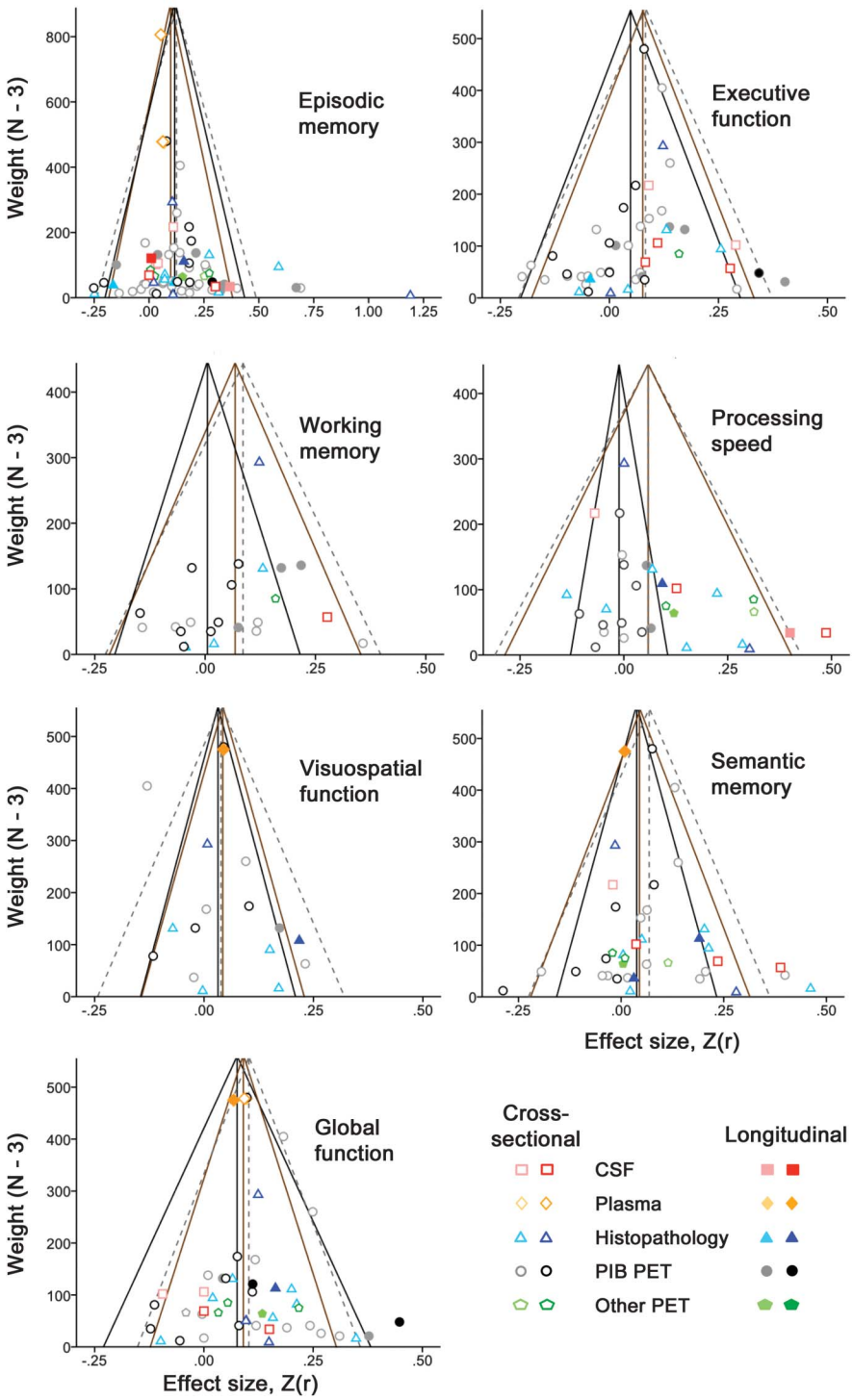
[c] Effect sizes for Rodrigue et al., 2012,[14] were computed using only the subsample of adults aged 60 years and older so as to be most comparable to the other studies (K. Rodrigue, personal communication, 2012).

[d] Effect sizes for Mielke et al., 2012,[50] were computed using the 1.5 PiB threshold.

[e] Only 47 subjects had available data for the memory measure in Gomperts et al., 2012[51] (S. Gomperts, personal communication, 2012).

[f] Effect size for Gu et al., 2012,[23] was computed by comparing the highest and lowest Aβ tertiles.

Figure 1 Funnel plots showing effect size as a function of study weight for each cognitive domain



Effect size is the Fisher *z* transform of Pearson *r*. Weight was computed by inverse variance weighting (for *r*, $w = n - 3$). Vertical lines indicate the weighted mean effect size; angled lines are anchored at ±3 SDs from the mean. Dark symbols (red, orange, blue, black, green) indicate studies selected as having independent cohorts; light symbols (pink, peach, aqua, gray, light green) indicate studies not so selected. Open symbols indicate cross-sectional studies; filled symbols indicate longitudinal studies. Solid black lines indicate the mean and ±3 SDs for studies using Pittsburgh compound B (PiB) and selected as independent cohorts; solid brown lines indicate these for all studies selected as independent cohorts; dashed gray lines indicate these for all studies.

except global function ($p = 0.19$). Results in the subset of studies using PiB imaging only were not significantly altered when not limited to 1 study per cohort in each domain (all p values >0.07).

Results in independent cohorts. Additional analyses were conducted using all 34 studies with independent cohorts, representing a maximum of 3,495 subjects (table 2, right). Significant effect sizes were observed

Table 2 Effect size statistics

	PiB only					Independent cohorts				
Cognitive domain	N	n	*r*	SD	*z*	N	n	*r*	SD	*z*
Episodic memory	10	1,260	0.12	0.11	2.87[a]	23	3,495	0.10	0.09	4.25[a]
Executive function	10	1,278	0.05	0.08	1.71	16	1,915	0.08	0.09	3.31[a]
Working memory	8	594	0.01	0.07	0.12	11	1,038	0.07	0.10	2.15
Processing speed	8	690	−0.01	0.04	−0.29	15	1,418	0.06	0.12	1.80
Visuospatial	4	876	0.03	0.06	0.93	7	1,761	0.04	0.06	1.64
Semantic memory	7	1,062	0.04	0.07	1.22	17	2,406	0.05	0.09	1.97
Global function	9	1,136	0.08	0.10	1.85	21	3,036	0.09	0.07	4.93[a]

Abbreviations: FDR = false discovery rate; N = number of analytic datasets; n = number of subjects across datasets; PiB = Pittsburgh compound B; *r* = weighted mean effect size (calculated with inverse Fisher *z* transform); SD = weighted standard deviation.
[a] $p_{FDR} < 0.05$.

for episodic memory, executive function, and global function, whereas working memory, processing speed, visuospatial function, and semantic memory did not have a significant effect size. Although episodic memory had the largest effect size, it was of similar magnitude to that of global function.

Because the utility of plasma as a biomarker of brain levels of amyloid-β is still undetermined,[17] and the studies using plasma markers[22–24] were among the most highly weighted because of their large sample sizes, we examined the results excluding these studies. Results were almost identical, with no meaningful change in the effect size or significance for any domain.

No significant effects were found for variability across amyloid assessment methods (CSF/plasma, histopathology, or PET imaging), study design (cross-sectional or longitudinal), or whether control variables were included or not (see e-Results).

The primary difference in this analysis compared with that including only PiB studies involved executive function, working memory, and processing speed. This may suggest a difference among amyloid assessment methods for these domains; however, no direct comparisons between PiB and all other methods reached the false discovery rate–corrected significance threshold for any domain (see e-Results).

DISCUSSION The results indicate that increased amyloid burden is associated with decreased cognitive performance in individuals without a diagnosis of mild cognitive impairment or dementia. The profile of performance associated with amyloid burden was that episodic memory and global cognitive function consistently had the largest, albeit still modest, effect sizes, whereas executive function, working memory, processing speed, visuospatial function, and semantic memory exhibited relatively smaller effect sizes with more inconsistency across analyses. It is important to note that even the largest mean effect sizes observed are considered small effects,[25] accounting for less than 2% of the total variance in cognitive performance and corresponding to Cohen $d = 0.24$. This is much smaller than effects ($d = 1.03$ for memory and 1.07 for executive function, corresponding to $r \approx 0.46$) observed in a meta-analysis of longitudinal studies of individuals later converting to AD without respect to amyloid pathology.[26] Although variability or measurement error in either the cognitive or amyloid variables could reduce the ability to detect the truth of a more substantial association, if the true correlation is within this range, it suggests that much larger samples than typically reported (e.g., n = 428 for detection of $r = 0.12$ with 80% power) are necessary for investigations of amyloid-cognition relations. Hence, large programmatic datasets or multicenter studies are most likely to yield informative data, and clinical trials on treatments for cerebral amyloidosis using cognitive outcomes must be appropriately powered, attempt to identify specific cognitive variables with larger effect sizes, or examine subpopulations (such as those with the highest amyloid burden) in which effect sizes may be larger. Our findings indicate that small but nontrivial differences in cognitive performance, especially memory performance, while an individual remains in the normal range may be an indication of amyloid burden associated with preclinical AD. However, it should be noted that these results do not show that amyloid burden is the pathophysiologic cause of such cognitive effects, only that it is correlated with cognition, and do not contradict theories that tau or other pathophysiologic processes are involved in the causal chain.

The current results provide only partial support for hypotheses that amyloid pathology has a greater influence on memory-related systems than on other cognitive domains.[27,28] Episodic memory had the largest and most significant effect size of the specific domains across all analyses. In the most methodologically homogeneous subset (studies using PiB imaging), episodic memory had a significantly larger effect size than executive function, working memory, processing speed, visuospatial function, or semantic memory. Of the other specific cognitive domains, only executive function had a significant effect size in the full independent cohorts analysis. Studies not using biomarkers of amyloid have suggested that measures of executive function may predict subsequent decline toward dementia,[29] although changes in executive function may occur later, relative to memory decline, in preclinical AD.[30]

Global cognitive function had an effect size approximately as large as episodic memory across analyses and so may provide an important indicator

of the earliest influences of amyloid on cognition. Because of ceiling effects on many measures of global cognition among cognitively normal individuals, very small differences may be meaningful. The measures of global cognition in our analyses, with 1 exception,[14] included a submeasure of episodic memory. It is possible that memory provides an outsized contribution to the relation of global cognition and amyloid burden within cognitively normal adults. Additionally, multiple studies reporting only global cognition were excluded[31–33] and this may bias the reported estimates for this domain.

The evident homogeneity in all domains and the pattern of spread in the funnel plots indicate relatively little evidence of publication bias. Given intense interest in the relationship between amyloid burden and cognition in preclinical populations, multiple reports prominently include negative findings. We attempted to mitigate bias by contacting authors when effect size estimates could not be derived from a publication. Effect sizes reported here may nonetheless represent the high end of expected relationships given the assumptions of our analysis. However, it remains possible that a critical level of amyloid burden may be necessary before neurodegeneration and cognitive change occur. If this is the case, the reported effect sizes may be an underestimate because most cognitively normal subjects have little to no amyloid burden, whereas the effects may be primarily driven by the subset of subjects with very high levels of amyloid.

There were several sources of variance among studies, including differences in amyloid assessment method, cross-sectional vs longitudinal study designs, and inclusion of control variables. However, the impact of these differences was modest, with considerable consistency of estimated effect sizes across methods. Potential exceptions to this were trends for smaller effect sizes in executive function, working memory, and processing speed using PiB rather than other measures. It will be important to reconcile the findings across methods to determine the extent to which amyloid burden truly affects executive function and its components or speed, and whether certain PET amyloid imaging techniques, as indirect measures of fibrillar plaque load, may provide a less sensitive indicator of amyloid's effect on some cognitive domains. Nonfibrillar and soluble oligomers of amyloid-β, not measured by current PET methods, are also likely present in preclinical individuals with fibrillar amyloid burden and could contribute to the cognitive effects observed.[34] Additionally, the PET imaging studies were dominated by a single tracer (PiB), with only 1 study for florbetaben and 3 for florbetapir. More studies with these and other markers will be necessary to determine whether the cognitive profile observed across PET tracers is consistent. Another caveat is that the longitudinal studies available are limited, with modest sample sizes and relatively short follow-up intervals. More long-term longitudinal studies are necessary before any firm conclusions can be drawn regarding the utility of tracking cognitive change in relation to amyloid burden.

The impact of age on cognition has been estimated as having much larger effect sizes than those seen here for amyloid burden, ranging from $r = 0.23$ in episodic memory to $r = 0.37$ in processing speed for adults aged 50 years and older.[35] Some portion of the age-related impact on cognition is likely attributable to influences of amyloid on cognition, although aging often remains significantly associated with cognition even when controlling for amyloid.[12,14,36] Even if all amyloid-related variance in memory performance estimated here was shared with the age-related variance in memory, approximately 50% of the age-related variance would remain unexplained. The correlation between age and amyloid in cognitively normal adults is likely to be approximately 0.3 to 0.4[36,37]; therefore, a more likely estimate is that approximately 80% of the age-related variance will remain unexplained by amyloid burden. It is likely that genetic factors, such as *APOE* allele status, will affect the relationship among aging, amyloid burden, and cognition.[37–40] Additionally, the preclinical impact of other types of age-related neurodegeneration on cognitive function during aging remains an important area of exploration.[41–45]

The studies analyzed primarily involved assessments of amyloid burden without regional specificity. CSF and plasma measures are by nature nonlocalizable, whereas PET imaging and histopathology studies often use a measure of global burden or large-scale regions of interest covering multiple neocortical areas. The widespread distribution of amyloid burden across the neocortex may account for the potential impact on multiple domains of cognitive function. However, more detailed investigation of relationships between regional amyloid deposition and cognitive domains is warranted.

The influence of amyloid on cognition seems to be of small, but nontrivial, magnitude. Episodic memory had a somewhat larger relationship to amyloid burden than did other specific cognitive domains, although it had a similar effect size as global cognitive function. Executive function had a significant relationship to amyloid burden only when combining across methods, indicating possible inconsistency across assessments. The clinical utility of such small effects is unclear, but knowing the cognitive profile of the subtle impact of amyloid burden before clinical impairment is observed may aid development of markers of preclinical AD or lead to outcome measures for clinical use.

AUTHOR CONTRIBUTIONS

Trey Hedden, PhD: drafted the manuscript, conceptualized and designed the study, analyzed and interpreted the data, acquired data, performed statistical analysis, and coordinated the analysis. Hwamee Oh, PhD: revised the manuscript, conceptualized and designed the study, analyzed and interpreted data, and acquired data. Alayna P. Younger, BA: revised the manuscript, acquired data, and analyzed data. Tanu A. Patel: acquired data and analyzed data.

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