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APOE ε4 and cognitive function in early life: A meta-analysis

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Abstract

Introduction. It is well established that the Apolipoprotein E (*APOE*) ε4 allele is associated with cognitive impairment and Alzheimer's disease in old age. By contrast, several studies have demonstrated cognitive benefits in young ε4 carriers. It is therefore possible that the ε4 allele exhibits a pleiotropic association with cognition across the lifespan where ε4-related benefits in youth reverse in later life to become risk factors for cognitive impairment and dementia in later life. To date though, there has been no broad quantitative review of work assessing *APOE*-cognition associations in children, adolescents and young adults.

Methods. Based on 20 studies investigating cognitive performance in ε4 carrying young persons and their non- ε4 counterparts, a meta-analytic study was conducted to examine *APOE* ε 4-related differences in cognitive performance. Additionally, we assessed whether the level of executive demands affected the strength of association between the ε4 allele and cognitive measure.

Results. In all analyses, estimated *APOE* ε4 related population effect sizes did not reliably differ from zero. Furthermore, the level of executive demands of the task did not affect this finding.

Conclusion. We found no *APOE* ε4-related cognitive benefits in young adults, adolescents, and children and findings were not moderated by the level of executive demands in a cognitive task. Given the current empirical evidence therefore, suggestions that *APOE* ε4 exhibits a pleiotropic association with cognition across the lifespan should be treated with caution.

Key words: Apolipoprotein E; *APOE*; cognition; cognitive performance; executive processes; young adults; adolescence; childhood; meta-analysis

Apolipoprotein E (*APOE*) is a protein that plays an important role in cholesterol transportation (for reviews of the mechanisms and functions of *APOE* in the nervous system, see Czyzewski, Pfeffer, & Barcikowska, 1998; Harris et al., 2003; Lahiri, Sambamurti, & Bennett, 2004; Mahley, 1988; Menzel, Kladetzky, & Assmann, 1983; Rocchi, Pellegrini, Siciliano, & Murri, 2003; Rubinsztein, 1995). The gene coding for *APOE* is located on chromosome 19 and has three alleles, ε2, ε3, and ε4.

APOE ε4 is well established as a risk factor for Alzheimer's disease (AD: Corder et al., 1993; Saunders et al, 1993), where persons possessing the ε4 allele have a three to four times higher risk for developing AD (see also Farrer et al., 1997, for a meta-analysis on effects of age, sex, and ethnicity on the association between *APOE* genotype and AD). Moreover, various studies have found that *APOE* ε4 is strongly associated with cognitive decline among persons who have been diagnosed with AD (e.g., Hirono, Hashimoto, Yasuda, Kazui, & Mori, 2003; Marra et al., 2004; Martins, Oulhaj, De Jager, & Williams, 2005; Plassman & Breitner, 1996). In addition, more than a decade of research has also demonstrated deficits in various cognitive domains in non-demented ε4 carriers in comparison with non- ε4 carriers in middle and old adulthood (e.g., Berr et al., 1996; Cantu, 2000; De Blasi et al., 2009; Driscoll, McDaniel, & Guynn, 2005; Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Helkala et al., 1995; Lavretsky et al., 2003; Negash et al., 2007; Packard et al., 2007; Reed et al., 1994; Small et al., 1999; Wetter et al., 2005; Zehnder et al., 2009). Conversely though, there is also evidence that cognitive performance is not affected by ε4 genotype in healthy adulthood (e.g., Bathum et al., 2006; Bunce, Fratiglioni, Small, Winblad, & Backman, 2004; Chen et al., 2002; Garcia et al., 2008; Jacobson et al., 2005; Kim et al., 2002; Marquis et al., 2002; Salo et al., 2001; Tohgi et al., 1997; Ystad et al., 2009), or that older ε4 carriers even show better cognitive performance (e.g., Carrion-Baralt et al., 2009). Thus, research on *APOE* ε4 in non-clinically impaired cognitive functioning has produced mixed findings. Yet, in their recent meta-analytic review on this issue, Wisdom, Callahan, and

Hawkins (2011) could somewhat resolve the inconsistency in the mixed pattern. Despite the heterogeneity on the single study level, overall, they showed that in middle and old age, ε4 carriers generally perform worse on cognitive measures, particularly in executive functioning, perceptual speed, and overall global cognitive ability relative to non- ε4 carriers. This is largely consistent with an earlier meta-analysis (Small, Rosnick, Fratiglioni, & Backman, 2004).

While the main focus of previous research has been on the association between *APOE* ε4 and cognitive impairment or AD in old age, recently research interest has turned to relations between *APOE* ε4 and cognitive performance in *young age*. Here, evidence has emerged that healthy young adults and children carrying the ε4 allele may in fact exhibit *better* cognitive performance relative to non-ε4 carriers (e.g., Acevedo, Piper, Craytor, Benice, & Raber, 2010; Alexander et al., 2007; Bloss, Delis, Salmon, & Bondi, 2010; Marchant, King, Tabet, & Rusted, 2010; Mondadori et al., 2007; Puttonen, Elovainio, Kivimaki, Lehtimaki, & Keltikangas-Jarvinen, 2003; Schultz et al., 2008; Wright et al., 2003; Yu, Lin, Chen, Hong, & Tsai, 2000). Equally though, there are studies which did not find differences in cognitive performance between young ε4 and non-ε4 carriers (e.g., Deary et al., 2003; Jorm et al., 2007; Luciano et al., 2009; Richter-Schmidinger et al., 2011; Ruiz et al., 2010; Taylor et al., in press; Turic, Fisher, Plomin, & Owen, 2001). In fact, there is also evidence that children and adolescents carrying the ε4 allele show poorer cognitive performance (e.g., Bloss, Delis, Salmon, & Bondi, 2008). In consequence, there is considerable debate as to whether *APOE* ε4 is associated with elevated cognitive performance in young age. This debate also calls for an overall qualitative assessment of available data which was the main aim of the present study.

The possibility that *APOE* ε4 confers cognitive benefits in youth while becoming a risk factor for cognitive impairment and AD in later life is of considerable theoretical interest. Han and Bondi (2008), together with other authors (e.g., Alexander et al., 2007; Wright et al.,

2003), argue that the relationship between the *APOE* ε4 allele and cognition across the lifespan is an example of *antagonistic pleiotropy*, a concept from evolutionary biology suggesting that individual alleles have different effects on fitness at different ages (Williams, 1957). In early life, a particular genotype may have benefits for survival and selection, while in old age it may become a risk factor for disease and senescence. However, although there is evidence of cognitive benefits in young persons consistent with the idea that a pleiotropic association exists between *APOE* ε4 and cognition across the lifespan, there are also studies that do not support this association.

One moderating factor that may explain the mixed findings is the cognitive domain assessed. Wisdom et al. (2011) concluded that in cognitively intact middle aged and older adults, *APOE* ε4 adversely affects specific cognitive domains, particularly executive functioning, perceptual speed, and global cognition. Similarly, Han and Bondi (2008) suggest that increased activation in frontal brain regions might mediate the cognitive advantages in young *APOE* ε4 carriers. Support for this idea comes from Marchant et al. (2010), who demonstrated ε4 benefits in tasks requiring executive control, whereas in "non-executive" tasks, no differences between young ε4 and non-ε4 carriers were detected. Therefore, it is possible that the degree of involvement of executive processes in task performance is related to the strength of association with the ε4 allele in younger persons. However, so far, no study has directly addressed this possibility and the present metaanalysis set out to initially explore this general proposal.

Taken together, because up to date, there has not been a quantitative review of the available empirical data on associations between possession of the ε4 allele and cognition in young persons, we conducted a meta-analysis addressing the association between *APOE* genotype and cognition in healthy young adults, adolescents and children and exploring the possibility that the extent to which a cognitive task is supported by executive processes may account for the strength of that association.

Methods

Selection of studies. A computer-based search involving PsycInfo, PubMed, Web of Science, and Psyndex was conducted using the terms 'APOE', 'Apolipoprotein E', 'cognitive performance', 'cognition', and 'memory'. In addition to using electronic databases, the reference lists of studies identified during the computer search were examined. To locate any potentially overlooked studies, articles citing the located studies were identified and checked for inclusion. The latest search for studies to be included was done on June 18, 2011.

Eligibility criteria. Studies included in the meta-analysis had to fulfil the following criteria. (1) The study investigated groups of *APOE* ε4 and non-ε4 carriers (i.e., genotypes were coded for presence or absence of at least one copy of the ε4 allele). (2) Participants had to be healthy and cognitively intact. Clinical subgroups (e.g., participants with diagnosed cognitive impairments, traumatic brain injuries, or concussions earlier in life) were excluded. (3) Mean ages of the investigated groups were permitted to vary between 5 and 35 years. (4) The study included at least one standardized measure of cognitive performance and reported sufficient statistical information to allow the calculation of effect sizes (e.g., means, standard deviations and sample sizes). Although some studies (i.e., Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Filippini et al., 2011) matched all these criteria, they were not included because the respective samples overlapped with those already included. In these cases, the study that provided the largest and most suitable sample was selected for inclusion.

Calculation of effect sizes. Effect sizes were calculated using Hedges' *g* (i.e., the difference in mean cognitive performance scores between the *APOE* ε4 and the non-ε4 groups divided by the pooled standard deviation) which was then transformed to the unbiased estimate Hedges' *d*, because the former measure overestimates effect sizes, particularly in small samples (DeCoster, 2004; Rustenbach, 2003)[1]. Accurate calculation of effect sizes

[1] Two technical details should be noted: First, including dependent effect sizes in the meta-analysis was avoided in order to meet the assumption of statistical independence between effects. Therefore, multiple effect sizes were permitted from the same study only in cases when subgroups were created within a particular experiment as long

depends on the availability of key information, including number of participants, cognitive performance means for each group, and their accompanying standard deviations or standard errors. If these data were not reported, Hedges' *g* was computed from either *t* statistics, *F* statistics with one degree of freedom in the numerator, chi-square statistics, or dichotomous dependent variables (cf. DeCoster, 2004). If it was not possible to derive effect sizes from the information reported in articles, we contacted authors and requested the relevant data. In five studies (i.e., Bloss et al., 2008; Bloss et al., 2010; Jorm et al., 2007; Marchant et al., 2010; and Taylor et al., in press), the participant numbers were not equal across the cognitive tasks due to missing data. In these cases, *N*-weighted means of Hedges' *g* were calculated before deriving a single Hedges' *d*.

Analytic strategy

We adopted two approaches to the modelling. First, all cognitive tasks were pooled, without classifying according to cognitive domain. Second, cognitive tasks were categorized according to whether they were high or low executive tasks.

Overall cognitive performance analysis. Here, individual effect sizes (Hedges' *d*) were pooled to derive the weighted average effect size *d*• across all studies as an estimation of the *APOE* ε4-related population effect size (Hedges & Olkin, 1985; Rustenbach, 2003). To assess the validity of the resulting meta-analytic model, the chi-square statistic, Q_T, was calculated to

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as the groups differed from one another in terms of participants sampled. Additionally, if a study included more than one measure of cognitive performance, the arithmetic mean of multiple dependent effect sizes Hedges' *g* was calculated before deriving a single effect size Hedges' *d* (cf. DeCoster, 2004). Second, in general, there is a distinction between fixed and random effects in meta-analyses (Hedges & Olkin, 1985; Shadish & Haddock, 1994). Statistically, the key difference is in the calculation of standard errors and confidence intervals, which for random effects models are typically much larger, as an additional variance component which represents the interaction between studies and their respective effect sizes is taken into account (Rustenbach, 2003). Thus, random effects models are more conservative, but yield more generalizable parameter estimates, whereas fixed effects models may lead to inappropriately strong conclusions: The included studies obviously differ in many features, for example in terms of sample size, mean age and age span of participants, gender and genotype frequencies, and method of genotyping etc. Thus each study estimates a population effect size, which is specific for its combination of features (i.e. studies may come from different study populations). Using the random effects meta-analytic model, it is possible to estimate the "global" population effect size underlying the distribution of study-estimated population effects. We argue that the aforementioned features may be important and not reflect simply noise error as it would be treated in fixed effects modelling. For this reasons, random effects models were used in the present study. However, we also repeated the analyses using less conservative fixed effects models to test whether this affected the pattern of results.

test for total homogeneity among effect sizes. If significant, it indicates that the observed studies are likely to have come from multiple populations. That is, there may be other characteristics affecting the magnitude of effect sizes (Hedges & Olkin, 1985). As a non-significant *Q* statistic alone does not indicate homogeneity, especially in small samples with low statistical power (Higgins, Thompson, Deeks, & Altman, 2003), the I^2 index was calculated as a measure of the degree of inconsistency in study findings. This represents the percentage of variance across studies not attributable to chance alone. The principal advantage of I^2 is that it does not inherently depend on the number of studies included in the meta-analysis and is therefore a more reliable approach to quantifying heterogeneity (Higgins et al., 2003).

High and low executive task analysis. The second meta-analysis explored the general proposal that executive demands of a cognitive task may moderate the strength of APOE ε4 associations with cognitive performance. Note that this relatively broad approach was chosen as (A) this hypothesis is the overlapping tenor of several conceptual proposals in the literature (e.g., Han & Bondi, 2008; Marchant et al., 2010) and (B) the still somewhat limited amount of available empirical studies does presently not allow for more detailed task- or process specific analyses on a metaanalytic level.

Hence, the cognitive tasks in each study were classified into two groups: high and low executive. Examples of tasks which primarily place demands on executive processes are word fluency, working memory, and switching or go/no-go tasks. Broadly, we used Miyake and colleagues' (2000) framework to determine which cognitive tasks were primarily "high executive". There are also tasks, that draw on executive processes at a lower level. Examples include measures of episodic memory and IQ. These types of task we refer to as "low executive". Note: As each cognitive task consists of several components, it is obvious that it is a mixture of executive and non-executive elements.

Classifications were made by two of the authors. This resulted in agreement for 93 of 97 classifications (inter-rater reliability, Cohen's κ =.88, $p < .001$). The four classifications for which there was disagreement were referred to another colleague. The final classification of each task is shown in Table 2. From the 20 studies that met the inclusion criteria, a total of 97 effect sizes Hedges' g were calculated: 20 for high and 77 for low executive tasks.

In the first analysis, no distinction in cognitive domain was made. Thus, for studies which reported multiple measures to assess cognitive performance for the same samples, all of the dependent effect size estimates, Hedges' *g*, were averaged and transformed into Hedges' *d* to derive a single effect size for each study. Here in the second analysis, these dependent effect size estimates, Hedges' *g*, were averaged across high and low executive tasks, to derive separate effect sizes (Hedges' *d*) for each cognitive domain within each study (see Table 2).

Then, individual effect sizes Hedges' *d* were pooled to derive weighted average effect sizes $d_{\bullet}$ across all studies for the high and low executive subgroups separately to obtain an estimation of their respective *APOE* ε4 related population effect sizes. Differences in the magnitude of these two population effect sizes were examined with a *z* test (cf. Rustenbach, 2003). If statistically significant, it indicates that the level of executive demand affects *APOE* ε4-related differences in cognitive performance.

Further moderating factors. Further moderators and mediators on *APOE* ε4-related differences in cognitive performance in young age were explored (i.e., age of participants and sample size). Therefore, we inspected scatter-plot diagrams plotting values of the respective factor against the corresponding effect sizes Hedges' *d*. Additionally, correlation analyses were carried out between those moderators and both weighted and non-weighted effect sizes.

Results

In the initial analyses, all cognitive tasks were grouped together irrespective of executive task classification and effect sizes computed. In the second stage of the analyses,

cognitive tasks were classified as either high or low executive tasks and effect sizes calculated for each category. Unless otherwise stated, effect sizes refer to Hedges' *d*.

Overall cognitive performance

In total, data from 11,098 non-overlapping participants were included in the analysis (3,034 *APOE* ε4 and 8,064 non-ε4 carriers). The weighted average mean age for the total sample was 14.5 years (range = 9.0 to 31.0 years). Table 1 presents all 20 study-level effect sizes for *APOE* ε4-related differences in cognitive performance. Positive values of *d* indicate better performance of *APOE* ε4 carriers, whereas negative values indicate better performance of non-ε4 carriers. Individual effect sizes ranged from -.25 to .37. Only one of the 20 study-level effects was reliably greater than zero (i.e., Schultz et al., 2008). The weighted average effect size of *APOE* genotype group across all effects was $d\bullet$ = .03 (*SD* = .02). This estimated *APOE* ε4-related population effect size did not reliably differ from zero (z = 1.41, p = .158; 95% CI for $d\bullet$ -.01 to .07). There was low heterogeneity among effect sizes ($Q_T(19)$ = 14.98, p = .724; I^2 = 0.0%). In Figure 1, study-level effect sizes are plotted against sample sizes for each of the investigations in Table 1. It can be seen that with increasing sample size, effects are closer to zero. The mean age of the study samples did not correlate significantly with either weighted or non-weighted effect sizes.

Insert Table 1 and Figure 1 about here

High and low executive tasks

In the second step of the analyses, cognitive tasks were classified according to whether they were high or low executive. The resulting 26 study-level effect sizes are presented in Table 2. Overall, individual effect sizes ranged from -.25 to .64. Only one of the 26 study-level effect sizes was reliably greater than zero (i.e., Schultz et al., 2008). The weighted average effect size of *APOE* genotype group across all effects was $d\bullet$ = .03 (*SD* = .02). This

estimated *APOE* ε4-related population effect size did not reliably differ from zero (z = 1.90, p = .057; 95% CI for d• -.01 to .07). There was a low level of heterogeneity among effect sizes (Q_T(25) = 20.22, p = .735; I^2 = 0.0%). The association between sample size and effect sizes is presented in Figure 2. Again, it can be seen that with increasing sample size, respective Hedges' d are closer to zero.

Of the 20 studies, there were eight effect sizes calculated for the high executive and 18 for the low executive subgroup. Individual effect sizes for the high executive subgroup ranged from -.17 to .17, and from -.25 to .64 for the low executive subgroup. None of the study-level effect sizes for the high executive subgroup was reliably greater than zero. However, one of the effect sizes for the low executive tasks (i.e., Schultz et al., 2008) was reliably greater than zero. The weighted average effect sizes of *APOE* genotype across the respective groupings were d• = .04 (SD = .03) and d• = .03 (SD = .02) for the high executive and low executive subgroups, respectively. None of these estimated *APOE* ε4-related population effect sizes differed reliably from zero (high executive subgroup: z = 1.37, p = .171; 95% CI for d• -.01 to .09; low executive subgroup: z = 1.34, p = .180; 95% CI for d• -.01 to .07). There was low heterogeneity among effect sizes within the high executive subgroup (Q_W(7) = 2.00, p = .960; I^2 = 0.0%) and low executive subgroup (Q_W(17) = 18.17, p = .378; I^2 = 6.4%). Overall, when the two groups were aggregated, the heterogeneity was low (Q_W(24) = 20.16, p = .687; I^2 = 0.0%. There was no significant difference in the magnitude of estimated *APOE* ε4-related population effect sizes between high and low executive tasks (z = .17, p = .864). Age did not correlate significantly with either weighted or non-weighted effect sizes for high and low executive tasks.

All of the foregoing analyses were rerun having excluded the fMRI studies as in such studies experimental groups usually are matched on several variables (e.g., cognitive performance) to disentangle neuronal differences (i.e. this is a less conservative approach of the present meta-analysis). This did not substantially alter the main findings. Additionally, all

of the findings reported above were derived by using random effects models, noted for being conservative in the estimations they produce. Therefore, we repeated the analyses using the less conservative fixed effect method. This did not alter the pattern of results obtained.

Insert Table 2 and Figure 2 about here

Discussion

This is the first meta-analysis of the available empirical evidence on the association between the *APOE* ε4 allele and cognition in young persons. Overall, we did not find any support for the hypothesis that possession of the ε4 allele confers cognitive benefits in children, adolescents or young adults. In the combined analysis of 20 studies involving over 11,000 non-overlapping individuals, only one study-level effect size was significantly different from zero. When the analysis was repeated with cognitive tasks classified as high and low executive, this finding did not change greatly. There was no evidence that high executive tasks produced stronger effect sizes, and of 26 computations, the one that was reliably different from zero was low executive. Age had no bearing on the above findings, and neither did the inclusion of fMRI studies.[2]

Therefore, the suggestion that the *APOE* ε4 allele exhibits antagonistic pleiotropy in relation to cognition across the lifespan (Alexander et al., 2007; Han & Bondi, 2008; Wright et al., 2003) receives no support from the present findings. Although it is well established that possession of the ε4 allele is a risk factor for cognitive impairment and dementia in old age, these analyses produced no evidence to suggest the ε4 allele is associated with cognitive benefits in young persons.

[2] Additionally, we computed the "fail safe *N*" (using the Stouffer method, cf. DeCoster, 2004). This refers to the number of additional studies with null findings that would have to be included in the analyses so that the mean effect sizes would not be significantly different from zero. This analysis suggested that a sufficient number of studies had been included in the present meta-analyses to reliably estimate population effect sizes.

It is clear that there are inconsistencies in research findings on the effects of *APOE* ε4 on cognitive performance in the young. One reason for this may be variation in the statistical power for individual studies. Whereas some studies with large sample sizes, and therefore high statistical power, found no differences (e.g., Deary et al., 2003; Jorm et al., 2007; Taylor et al., in press), other studies with small sample sizes, and therefore lower statistical power, did find *APOE* ε4-related benefits (e.g., Acevedo et al., 2010; Marchant et al., 2010; Puttonen et al., 2003; Yu et al., 2000). Type I or II errors may explain some of the variation in findings, but generally studies with small *N*s tend to either over- or underestimate effect sizes, whereas investigations with large *N*s estimate effect sizes more accurately. It is of note that Figures 1 and 2 suggest that larger *N*s were associated with smaller effect sizes (see also Footnote 2). The point is underlined by the largest study to date to specifically test the pleiotropic effects of APOE in over 5,000 adults (Bunce et al., 2011). Here, no ε4-related benefits were found in a range of cognitive domains including perceptual speed, working memory, lexical decision making and episodic memory.

There are some limitations to the present investigation that should be acknowledged. First, as there was homogeneity within the various subgroups and, indeed, the total study sample, it suggests that the observed studies came from the same population (i.e., that there were no other characteristics affecting the magnitude of effect sizes). This makes detecting additional moderating factors difficult. An example is the distinction between individuals who are either heterozygous or homozygous for the *APOE* ε4 allele. Surprisingly few of the studies actually separately reported *APOE* genotype differences for ε3/4 and ε4/4 carriers, preventing the analysis of differential effects in those subgroups at present. This should be done in future work. Similarly, as only a few studies reported effect sizes for the interaction between *APOE* genotype and gender, we could not assess whether any *APOE* ε4-related benefits were gender specific. However, as cognitive benefits were found both in samples

consisting only of females (e.g., Yu et al., 2000) and only of males (e.g., Schultz et al., 2008), it is likely that there are no gender differences in associations where they exist.

Although our main conclusion is that the present findings do not suggest that possession of the ε4 allele benefits cognitive function in young adults, adolescents, or children, and therefore do not support a pleiotropic association between *APOE* ε4 and cognition across the lifespan, there are several caveats to these conclusions. First, more studies are needed, both cross-sectional, but importantly longitudinal, that demonstrate a positive relationship (or otherwise) between possession of the ε4 allele and cognition in young persons. Second, a number of functional brain imaging studies have recently emerged in young adults that suggest brain activity to vary according to possession of the ε4 allele (e.g., Filbey, Slack, Sunderland, & Cohen, 2006; Filippini et al., 2009; Reiman et al., 2004; Scarmeas et al., 2005). To our knowledge though, there are no fMRI studies to date demonstrating that ε4-related differences in brain activity are associated with benefits in cognitive performance. Such evidence would provide important insights into potential mediating mechanisms of any *APOE* ε4-related cognitive benefits. Third, it may be possible that the effects are process-specific and thus are only evident in tasks placing high demands on a specific set or constellation of (executive) processes (see e.g., Marchant et al., 2010, for the possibility that prospective memory requiring the interplay of memory, attention and executive control, Zeintl, Kliegel & Hofer, 2007, or single subscales such as the Mental Arithmetic Task that again requires the coordination of episodic memory, attention and working memory may be potential candidates). Yet, our analyses suggest that the category of executive demands that has been nominated in the literature may be too broad to test this assumption and thus more empirical studies delineating the effects of specific (executive and also non-executive) cognitive processes and their interplay are needed.

Regarding future research, it is important that longitudinal behavioral and functional imaging studies add to the body of work on any lifespan pleiotropic effects of *APOE* ε4 on

cognition. Longitudinal studies may provide important information as to the trajectory of cognitive change over time (ε4-related cognitive benefits in the young should decline and converge with non- ε4 carriers in middle age) and additional functional brain imaging studies in young adults may provide valuable insights concerning the neurobiological basis of ε4-related cognitive benefits where they exist. Until such research emerges, the proposal that *APOE* ε4 confers cognitive benefits to young person should be treated with caution.

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Table 1

Study-level effect sizes (Hedges' d) for all included studies. Positive values of d indicate better cognitive performance of APOE ε4 carriers (ε4+), and negative values of d indicate better performance of non- ε4 carriers (ε4-).

Study	Mean age	*N* ε4+	*N* ε4-	Task	Hedges' *d*	*p* value of Hedges' *d*	lower/upper 95%-Confidence Limit of Hedges' *d*
Acevedo et al. (2010)	9.0	12	38	Conner's Continuous Performance Test; Spatial Span (forward and backward); Dot Location Test; Memory Island; Family Pictures; Wechsler Abbreviated Scale of Intelligence (vocabulary and block design)	.27	.408	-.38/.92
Alexander et al. (2007)	16.9	50	174	6-30 years of age: Executive Maze; Visual Working Memory (reaction time and errors); Word Generation; Animal Naming	.10	.529	-.21/.41
Bloss et al. (2008)[a]	13.4	24	84	California Achievement Test; Rey Complex Figure Test (copy condition)	-.15	.539	-.62/.32
Bloss et al. (2010)[a]	13.3	32	113	California Achievement Test; Rey Complex Figure Test (copy condition)	.01	.957	-.40/.42
Deary et al. (2003)	11.0	42	131	Moray House Test	-.20	.258	-.55/.15
Filbey et al. (2006)[b]	25.5	8	8	Visual Working Memory Task (hits and reaction time)	-.07	.888	-1.05/.91
Filippini et al. (2009)[b]	28.5	18	18	Memory Test	.06	.862	-.59/.71
Jorm et al. (2007)[a]	22.6	573	1524	Digits Backwards Subtest of the Wechsler Memory Scale; Spot-the-Word Test; California Verbal Learning Test (immediate and delayed recall); Symbol-Digit Modalities Test; Reaction Time (simple and choice rt)	.01	.819	-.09/.11
Luciano et al. (2009)	11.0	279	668	Moray House Test	.03	.701	-.11/.17
Marchant et al. (2010)[a]	20.3	27	32	Spatial Working Memory Task; Verbal Fluency Task; Rapid Visual Information Processing; Decision-making Ability (card sorting); Prospective Memory Task; Immediate Verbal Free Recall; National Adult Reading Test	.37	.189	-.18/.92

Mondadori et al. (2007)	22.8	87	253	Delayed and Immediate Recall	.06	.630	-.18/.30
Puttonen et al. (2003)	28.0	20	37	Mental Arithmetic Task; Choice Deadline Reaction Time Task	.29	.294	-.26/.84
Reiman et al. (2004)[b]	31.0	12	14	Wechsler Adult Intelligence Scale-Revised; Auditory Verbal Learning Test; Complex Figure Test	-.04	.911	-.81/.73
Richter-Schmidinger et al. (2011)	24.6	18	117	IGT Test Battery	.04	.875	-.46/.54
Ruiz et al. (2010)	15.4	76	336	Spanish Version of the SRA-Test of Educational Ability (verbal. numeric. and reasoning abilities)	-.06	.645	-.31/.19
Scarmeas et al. (2005)[b]	23.5	4	16	Non-verbal Memory Task (simple demand and titrated demand condition); Selective Reminding Test; Wechsler Adult Intelligence Scale-Revised (digit-symbol modalities and vocabulary); National Adult Reading Test	-.25	.651	-1.35/.85
Schultz et al. (2008)	19.9	188	437	Armed Forces Qualification Test	.25(**)	.004	08/.42
Taylor et al. (in press)[a]	10.0	1486	3824	Wechsler Intelligence Scale for Children; Wechsler Objective Language Dimensions Test; Wechsler Objective Reading Dimensions Test; Nonword Repetition Test; Counting Span Working Memory Task; Nationally Administered School-based Test	.01	.786	-.06/.08
Turic et al. (2001)	10.0	52	143	Wechsler Intelligence Scale for Children. Revised	-.01	.955	-.33/.31
Yu et al. (2000)	20.0	26	97	Wechsler Adult Intelligence Scale-Revised	.33	.131	-.10/.76

Notes:
* = *APOE* ε4-related difference significant at $p = .05$; ** $p = .01$.

[a]Sample sizes varied slightly across the cognitive tasks. Reported number of participants refer to the cognitive task with the largest sample size in the study.

[b]Cognitive performance was assessed in subjects who also participated in an additional fMRI/MEG experiment.

Table 2

Study-level effect sizes (Hedges' d) for high and low executive tasks. Positive values of d indicate better cognitive performance of APOE ε4 carriers (ε4+), and negative values indicate better performance of non- ε4 carriers (ε4-).

Study	Mean age	*N* ε4+	*N* ε4-	Task	Classification	Hedges' *d*	*p* value of Hedges' *d*	lower/upper 95%-Confidence Limit of Hedges' *d*
Acevedo et al (2010)[c]	9.0	12	38	Conner's Continuous Performance Test; Spatial Span (backward)	high executive	-.10	.766	-.75/.55
	9.0	12[d]	38[d]	Spatial Span (forward); Dot Location Test; Memory Island; Family Pictures; Wechsler Abbreviated Scale of Intelligence (vocabulary and block design)	low executive	.64	.057	-.02/1.30
Alexander et al. (2007)	16.9	50	174	6-30 years of age: Executive Maze; Visual Working Memory (reaction time and errors); Word Generation; Animal Naming	high executive	.10	.529	-.21/.41
Bloss et al. (2008)[a]	13.4	24	84	California Achievement Test; Rey Complex Figure Test (copy condition)	low executive	-.15	.539	-.62/.32
Bloss et al. (2010)[a]	13.3	32	113	California Achievement Test; Rey Complex Figure Test (copy condition)	low executive	.01	.957	-.40/.42
Deary et al. (2003)	11.0	42	131	Moray House Test	low executive	-.20	.258	-.55/.15
Filbey et al. (2006)[b]	25.5	8	8	Visual Working Memory Task (hits and reaction time)	high executive	-.07	.888	-1.05/.91
Filippini et al. (2009)[b]	28.5	18	18	Memory Test	low executive	.06	.862	-.59/.71
Jorm et al (2007)[a,c]	22.6	573[d]	1523[d]	Digits Backwards Subtest of the Wechsler Memory Scale	high executive	.01	.843	-.09/.11
	22.6	573	1524	Spot-the-Word Test; California Verbal Learning Test (immediate and delayed recall); Symbol-Digit Modalities Test; Reaction Time (simple and choice rt)	low executive	.01	.815	-.09/.11
Luciano et al. (2009)	11.0	279	668	Moray House Test	low executive	.03	.701	-.11/.17

Marchant et al (2010)[a,c]	20.3	26[d]	29[d]	Spatial Working Memory Task; Verbal Fluency Task	high executive	.17	.585	-.46/.80
	20.3	27	32	Rapid Visual Information Processing; Decision-making Ability (card sorting); Prospective Memory Task; Immediate Verbal Free Recall; National Adult Reading Test	low executive	.40	.144	-.14/.94
Mondadori et al. (2007)	22.8	87	253	Delayed and Immediate Recall	low executive	.06	.630	-.18/.30
Puttonen et al. (2003)	28.0	20	37	Mental Arithmetic Task; Choice Deadline Reaction Time Task	low executive	.29	.294	-.26/.84
Reiman et al (2004)[b,c]	31.0	12	14	Wechsler Adult Intelligence Scale-Revised (controlled oral word association test)	high executive	-.11	.774	-.88/.66
	31.0	12[d]	14[d]	Wechsler Adult Intelligence Scale-Revised (digit span, mental arithmetic, similarities, information, block design, and orientation subtest of Wechsler memory scale); Auditory Verbal Learning Test; Complex Figure Test (copy, recall, and Boston naming test)	low executive	-.04	.925	-.81/.73
Richter-Schmidinger et al. (2011)[c]	24.6	18	117	IGT Tests Battery (working memory)	high executive	-.17	.505	-.67/.33
	24.6	18[d]	117[d]	IGT Tests Battery (learning ability, delayed recall, verbal memory, and visual memory)	low executive	.09	.716	-.41/.59
Ruiz et al. (2010)	15.4	76	336	Spanish Version of the SRA-Test of Educational Ability (verbal. numeric. and reasoning abilities)	low executive	-.06	.645	-.31/.19
Scarmeas et al. (2005)[b]	23.5	4	16	Non-verbal Memory Task (simple demand and titrated demand condition); Selective Reminding Test; Wechsler Adult Intelligence Scale-Revised (digit-symbol modalities and vocabulary); National Adult Reading Test	low executive	-.25	.651	-1.35/.85
Schultz et al. (2008)	19.9	188	437	Armed Forces Qualification Test	low executive	.25(**)	.004	.08/.42

Taylor et al. (in press)[a,c]	10.6	1486	3824	Counting Span Working Memory Task	high executive	.06	.114	-.01/.13
	10.0	1486[d]	3824[d]	Wechsler Intelligence Scale for Children; Wechsler Objective Language Dimensions Test; Wechsler Objective Reading Dimensions Test; Nonword Repetition Test; Nationally Administered School-based Test	low executive	.00	.908	-.06/.06
Turic et al. (2001)	10.0	52	143	Wechsler Intelligence Scale for Children. Revised	low executive	-.01	.955	-.33/.31
Yu et al. (2000)	20.0	26	97	Wechsler Adult Intelligence Scale-Revised	low executive	.33	.131	-.10/.76

Notes.
* = *APOE* ε4-related difference significant at $p = .05$; ** $p = .01$.

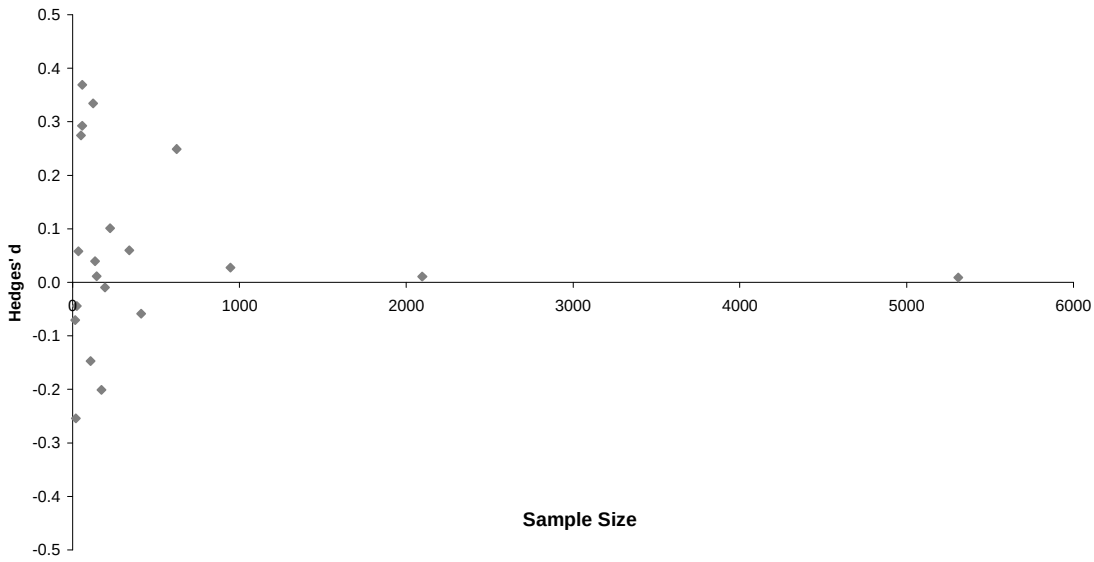
[a]Sample sizes varied slightly across the cognitive tasks. Reported number of participants refer to the cognitive task with the largest sample size in the study.

[b]Cognitive performance was assessed in subjects who also participated in an additional fMRI/MEG experiment.

[c]These studies reported multiple measures to assess cognitive performance for the same samples. For these studies, multiple effect sizes Hedges' *g* were separately averaged to a mean effect size for each of these three subgroups. Hence, in these cases a violation of the assumption of statistical independence of effect sizes was allowed.

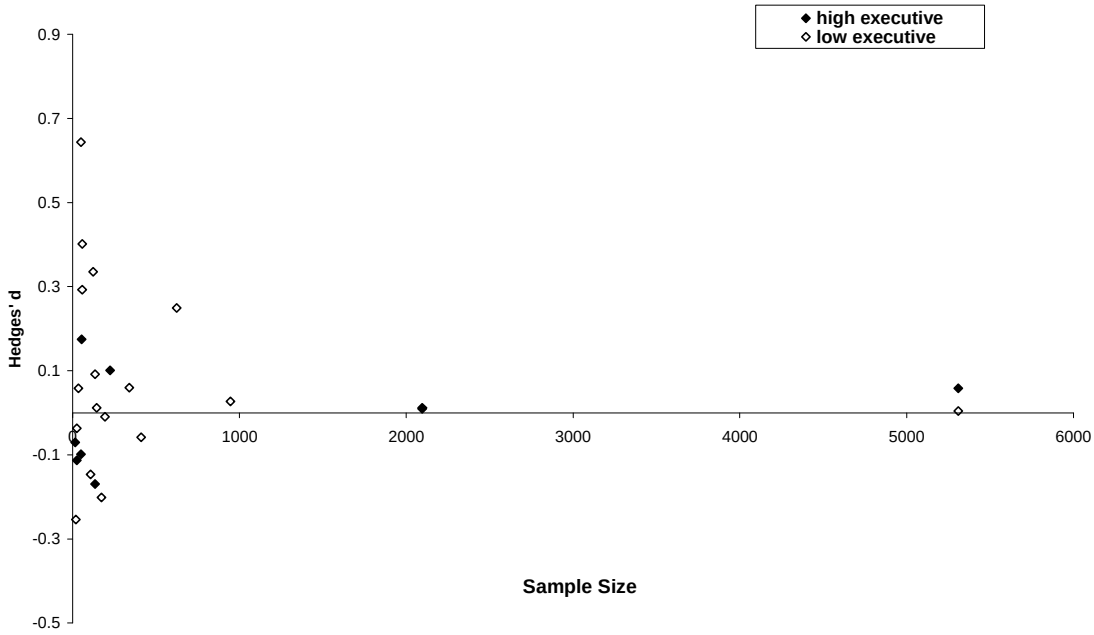
[d]These subjects are multiply listed in the table, because the respective studies reported multiple measures to assess cognitive performance for the same samples.

Figure 1. Effect sizes in the overall cognitive performance analysis.



Note. Non-weighted overall effect sizes (Hedges' *d*) plotted against total sample sizes.

Figure 2. Effect sizes in the high and low executive task analysis.



Note. Non-weighted effect sizes (Hedges' *d*) plotted against total sample sizes for high and low executive tasks (note that some of the plots are not visible as they overlap because the respective values are identical in both subgroups).