Unruptured intracranial aneurysm treatment effects on cognitive function: a meta-analysis

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OBJECTIVE The treatment of an unruptured intracranial aneurysm (UIA) is not free of morbidity and mortality, and the decision is made by weighing the risks of treatment complications against the risk of aneurysm rupture. This meta-analysis quantitatively analyzed the literature on the effects of UIA treatment on cognition.

METHODS MEDLINE, Embase, and PsycInfo were systematically searched for studies that reported on the cognitive status of UIA patients before and after aneurysm treatment. The search was restricted to prospective cohort and case-control studies published between January 1, 1998, and January 1, 2013. The analyses focused on the effect of treatment on general cognitive functioning, with an emphasis on 4 specific cognitive domains: executive functions, verbal and visual memory, and visuospatial functions.

RESULTS Eight studies, with a total of 281 patients, were included in the meta-analysis. Treatment did not affect general cognitive functioning (effect size [ES] –0.22 [95% CI –0.78 to 0.34]). Executive functions and verbal memory domains trended toward posttreatment impairment (ES –0.46 [95% CI –0.93 to 0.01] and ES –0.31 [95% CI –1.24 to 0.61]), and performance of visual memory tasks trended toward posttreatment improvement (ES 1.48 [95% CI –0.36 to 3.31]). Lastly, treatment did not significantly affect visuospatial functions (ES –0.08 [95% CI –0.30 to 0.45]).

CONCLUSIONS The treatment of an UIA does not seem to affect long-term cognitive function. However, definitive conclusions were not possible due to the paucity of studies addressing this issue.


KEY WORDS unruptured intracranial aneurysm; cognition; surgical clipping; endovascular coiling; vascular disorders
ever, the treatment of an intracranial aneurysm is not without risk of morbidity and mortality. The rate of mortality and neurological complications differs between the treatment modalities, with rates estimated at between 0.7% and 7.7% for surgical clipping and between 0.5% and 2.4% for endovascular coiling, respectively. Thus, the decision to treat a UIA is made by weighing the risks of treatment complications against the risk of aneurysm rupture.

The ISUIA was the first prospective study to define morbidity not only as functional disability, but also as neuropsychological impairment. Regardless of the time of assessment, type of treatment, or history of SAH, the rate of neuropsychological impairment was higher than that of functional disability, suggesting that a considerable proportion of morbidity after UIA treatment is due to neuropsychological impairment. This finding proposes that the decision to treat ought to also be informed by the cognitive outcomes of treatment. Since the ISUIA, several studies have investigated the effect of UIA treatment on cognition (see the study by Bonares et al.5 for a review).

To our knowledge, this meta-analysis is the first effort to quantitatively analyze the literature on the effects of UIA treatment on cognition. Cohort and case-control studies that reported on the cognitive status of UIA patients before and after treatment were sought. The analyses focus on the effect of treatment on general cognitive functioning and 4 specific cognitive domains: executive “frontal lobe” functions, verbal and visual memory, and visuospatial function.

**Methods**

**Study Selection Criteria**

MEDLINE, Embase, and PsycInfo were searched for articles that assessed cognitive outcome after UIA treatment using the key words “unruptured,” “aneurysm,” “UIA,” “coil,” and “clip.” Appropriate wildcards were used in the search to account for plurals and variations in spelling. The literature was restricted to clinical studies published in the English language, between January 1, 1998, and January 1, 2013. The inclusion criteria captured studies of UIA patients who underwent treatment (either surgical clipping or endovascular coiling) and received cognitive testing both before and after treatment. Case studies, reviews, and conference abstracts were excluded.

**Data Synthesis and Analysis**

The systematic review and data extraction (sample size, age, aneurysm location, treatment type, time to posttreatment follow-up, cognitive tests used, and raw data) were independently performed by 3 researchers (M.J.B., P.E., and K.A.V.). The effect sizes were calculated using the inverse variance method and entered into random effects models. The neuropsychological assessments extracted from the eligible studies were divided into 4 cognitive domains: executive “frontal lobe” functions, verbal and visual memory, and visuospatial functions, as well as general cognitive functioning, to maximize the number of analyses and the amount of data in each study. The most representative and commonly used tests in the English language were chosen for each cognitive domain, based on consultations of a neuropsychology handbook and an experienced neuropsychologist.

A funnel plot was used to assess publication bias, and the methodological quality of the studies were assessed using the Newcastle-Ottawa Scale (NOS). The NOS is a checklist that provides a quantitative assessment based on participant selection, comparability, and outcomes. Issues with the NOS checklist have been discussed previously.

The statistical heterogeneity of the effects estimates was assessed using the I² test, which measures the percentage of variation across studies due to the differences between study results, rather than to chance. Data entry and analyses were performed using RevMan version 5.2 (the Nordic Cochrane Centre). The methods and findings reported in the present meta-analysis are based on the PRISMA guidelines.

**Results**

The process of the literature search is depicted in Fig. 1. The initial search yielded 2452 abstracts, from which 1035 duplicates were removed. The remaining 1417 studies were screened, and 1403 were excluded for not meeting the inclusion criteria outlined above, based on information found in the abstracts. Of the 15 full-text articles reviewed, 8 were excluded for the following reasons: lack of formal cognitive assessments, no pretreatment cognitive testing, not reporting usable data (i.e., pre- and post-treatment data). Of the 8 included studies, 1 was a case-control study and 7 were prospective cohort studies. The mean NOS score of 4.8 was fairly low, but due to the variability in the checklist-study compatibility, there was no common maximum score. The scores for individual studies and their respective maximum scores are depicted in Table 1. A total of 281 patients (mean age 54.0, range 15–77 years; 75% females) were included in the meta-analysis. A random-effects meta-analysis was performed on the effects of UIA treatment on: general cognitive function (Mini–Mental State Examination [MMSE]), executive functions (Trail Making Test Part B [TMT-B] and Color Word Interference Task [CWIT]), verbal memory (Auditory Verbal Learning Test [AVLT]), and Logical Memory [LM] from the Wechsler Memory Scale), visual memory (Rey-Osterrieth Complex Figure [ROCF], recall subtest), and visuospatial functions (Block Design and ROCF, copy subtest).

The forest plots are presented in Fig. 2. Treatment did not affect general cognitive functioning: the effect size (ES) was 0.22 (95% CI –0.78 to 0.34). A trend toward posttreatment impairment was found in executive function test performance: ES –0.46 (95% CI –0.93 to 0.01). Conversely, performance on visual memory tasks trended toward improvement following treatment: ES 1.48 (95% CI –0.36 to 3.31). A weak trend toward posttreatment impairment was found for verbal memory, with an ES of 0.31 (95% CI –1.24 to 0.61). Treatment did not significantly affect visuospatial functions: ES 0.08 (95% CI –0.30 to 0.45).

Results did not differ significantly when the coil-treated UIA patients were excluded from the meta-analyses for...
the executive function (ES $-0.37$ [95% CI $-1.04$ to $0.31$]) and verbal memory analyses (ES $-0.34$ [95% CI $-1.29$ to $0.62$]) (Table 2).

The statistical heterogeneity between studies ranged from low to high. Specifically, statistical heterogeneity was low to moderate among most studies (general cognition, $I^2 = 0%$; visual memory, $I^2 = 12%$; visuospatial ability, $I^2 = 48%$), with the exception of high statistical heterogeneity in the others (executive function, $I^2 = 61%$; verbal memory, $I^2 = 89%$).

A visual examination of the funnel plots did not indicate obvious publication bias in the executive, visuospatial, and global cognitive function domains (Fig. 3), although there was some evidence of bias in the verbal and visual memory domains (Fig. 4). A statistical test (e.g., Begg’s test) was not performed due to the small number of studies included in the meta-analysis, which entails low statistical power.

**Discussion**

While the risk of neurological disability and mortality associated with UIA treatment has been established, the cognitive sequelae thereof remain unclear. This meta-analysis set out to collect and quantitatively analyze the literature on the effects of UIA treatment on cognitive functioning. A trend toward posttreatment impairments in frontal executive functions (TMT-B and CWIT) and, conversely, a trend toward posttreatment improvement in visual memory functions (ROCF recall) were found. A weak trend toward posttreatment decline was also observed in the verbal domain (LM, CVLT-II, and AVLT). Treatment did not alter visuospatial functions (Block test and ROCF copy) or general cognition as assessed by the MMSE.

Neither of the studies using the MMSE found any difference in general cognition between pre- and posttreatment phases. It is possible that the MMSE as a test of general cognitive ability might not be sensitive enough to detect the subtle deficits associated with UIA. This proposal is supported by the finding that the MMSE is less sensitive for detecting stroke-related cognitive impairment compared with the Montreal Cognitive Assessment, which is another measure of general cognition and is specialized to detect mild cognitive deficits. Rather, a series of measures for different cognitive domains might be necessary to detect the unique pattern of cognitive impairment, as was demonstrated by the other analyses in this meta-analysis.

A potential reason for the improvement in cognitive function after UIA treatment is the alleviation of anxiety. Before treatment, a patient harboring an UIA may feel as though he/she is a “ticking time bomb.” In turn, this anxiety could result in cognitive impairment. This hypothesis finds evidence from studies that have demonstrated poor cognitive functioning in patients with anxiety disorder.

To the extent that anxiety impairs cognition in patients with untreated UIAs, the treatment of their aneurysms ought to allay anxiety and simultaneously improve cognition. There is preliminary evidence for this hypothesis.

Conversely, both major and minor treatment-linked damage (e.g., damage to adjacent gray or white matter or damage to blood vessel walls) may contribute to small deficits in cognitive functioning.

Bearing in mind the results of the meta-analyses collectively, from a cognitive perspective, it appears as though the risk of UIA treatment is generally low; however, this risk may not be zero. Consequently, although the majority of patients who undergo UIA treatment appear to do so cognitively unscathed, there may be some patients who do not. Therefore, the effect of patients whose cognition may have been significantly decreased by treatment may have been diluted by that of the majority of patients, in whom this was not the case. Consequently, at the sample level, cognition may appear to be spared by UIA treatment; however, this does not preclude the presence of cognitive impairment at the patient level.

This meta-analysis was hindered by several issues. First, the number of studies was small, with only 8 studies meeting the inclusion criteria. Consequently, the total sample size of the analyses was low (general cognitive ability, $n = 70$; executive function, $n = 117$; verbal memory, $n = 117$; visual memory, $n = 112$; visuospatial ability, $n = 112$). This reduced the statistical power of the analyses, introduced uncertainty into the results, and reduced the variety of cognitive domains that were tested, although the latter is also a result of the narrow range of neuropsychological tests used in the literature. For example, the
The paucity of studies forced the clumping of the domain of executive functions; a greater availability of data would have separated that into more focused domains such as attention control, decision making, and working memory.

Another issue is the bias in treatment approaches. All of the included studies treated the aneurysms by surgical clipping, except for 1 study, in which half of the patients (32/65) were treated by endovascular coiling. This pattern might be explained by the fact that most of the studies are older; 5 of the 7 included studies were from the 1990s.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Sample Size</th>
<th>Mean Age in Yrs (range)</th>
<th>Aneurysm Locations</th>
<th>Treatment Method</th>
<th>Time to Posttreatment Testing</th>
<th>Neuropsychological Tests</th>
<th>NOS Scores</th>
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</thead>
<tbody>
<tr>
<td>Haug et al., 2009</td>
<td>37</td>
<td>53.2 (42–63)</td>
<td>MCA</td>
<td>Surgical clipping</td>
<td>3 &amp; 12 mos</td>
<td>BD,* CVLT-II,* CWIT*, DFT, DSp, DSy, GP, M, ROCF,* S, TMT-B, V, VFT</td>
<td>6/9</td>
</tr>
<tr>
<td>Fukunaga et al., 1999</td>
<td>30</td>
<td>57.8 (38–73)</td>
<td>ACoA, ICA, B/SCA</td>
<td>Surgical clipping</td>
<td>1 mo</td>
<td>MMSE,* KH, MT</td>
<td>4/8</td>
</tr>
<tr>
<td>Kubo et al., 2010</td>
<td>28</td>
<td>71.6 (70–75)</td>
<td>ACoA, ICA, MCA</td>
<td>Surgical clipping</td>
<td>1 mo</td>
<td>ROCF,* WAIS-R, WMS</td>
<td>6/8</td>
</tr>
<tr>
<td>Otawara et al., 2005</td>
<td>44</td>
<td>56.8 (32–70)</td>
<td>ACA</td>
<td>Surgical clipping</td>
<td>1 mo</td>
<td>ROCF,* WAIS-R, WMS</td>
<td>5/8</td>
</tr>
<tr>
<td>Pereira-Filho et al., 2010</td>
<td>40</td>
<td>53.2 (22–70)</td>
<td>ACA, ACoA, CA, MCA, OA, PCoA</td>
<td>Surgical clipping</td>
<td>≥1 mo</td>
<td>MMSE*</td>
<td>5/8</td>
</tr>
<tr>
<td>Preiss et al., 2012</td>
<td>65</td>
<td>44.9 (15–59)</td>
<td>ACoA, ICA MCA, OA, PCoA, PC</td>
<td>Surgical clipping, endovascular coiling</td>
<td>1 yr</td>
<td>AVLT,* TMT-B*</td>
<td>4/8</td>
</tr>
<tr>
<td>Tuffiash et al., 2003</td>
<td>25</td>
<td>53.2 (32–67)</td>
<td>ACA, AChA, BA, ICA, MCA, OA, PCoA, SHA</td>
<td>Surgical clipping</td>
<td>1 wk</td>
<td>COWAT, GP, TMT-B,* ROCF,* WMS*</td>
<td>3/8</td>
</tr>
<tr>
<td>Hillis et al., 2000</td>
<td>12</td>
<td>49.6 (30–77)</td>
<td>ACA, AChA, ACoA, BA, ICA, MCA, PCoA, PeCA, PCA, SCA</td>
<td>Surgical clipping</td>
<td>3 mos</td>
<td>BD, COWAT, CWIT,* BNT, DSp, DSy, GP, AVLT,* RCF, WRMT, WMS</td>
<td>5/8</td>
</tr>
</tbody>
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ACA = Anterior cerebral artery; AChA = anterior circulation, anterior choroidal artery; ACoA = anterior communicating artery; AVLT = Auditory Verbal Learning Test; BA = basilar artery; B/SCA = basilar/superior cerebellar artery; BD = Block Design; BNT = Boston Naming Test; CVLT-II = California Verbal Learning Test II; CA = carotid artery; COWAT = Controlled Oral Word Association Test; CWIT = Color-Word Interference Test; DFT = Design Fluency Test; DSp = Digit Span; DSy = Digit Symbol; GP = Grooved Pegboard; ICA = internal carotid artery; KH = Kana-Hiroi; M = Matrices; MT = Maze Test; MCA = middle cerebral artery; MMSE = Mini–Mental State Examination; OA = ophthalmic artery; PC = posterior cerebral artery; PeCA = pericallosal artery; PCoA = posterior communicating artery; PICA = posterior inferior cerebellar artery; S = Similarities; SHA = superior hypophyseal artery; V = Vocabulary; VFT = Verbal Fluency Test; WRMT = Warrington Recognition Memory Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS = Wechsler Memory Scale.

* Used in meta-analysis.

![Fig. 2](image-url) **Fig. 2.** Forest plot of the mean weighted ESs with 95% CIs for the 5 cognitive domains. Executive functions, –0.46 (95% CI –0.93 to 0.01); verbal memory, –0.31 (95% CI –1.24 to 0.61); visual memory, 1.48 (95% CI –0.36 to 3.31); visuospatial functions, –0.08 (95% CI –0.30 to 0.45); and global cognitive functions, –0.22 (95% CI –0.76 to 0.34).
and 2000s, and only 3 were published in the 2010s. This presents 2 main concerns. First, while this meta-analysis is ostensibly a review of general aneurysm treatment, the overwhelming bias toward surgical clipping makes it more akin to a review of that specific treatment approach. Second, the current trend favors an endovascular approach over surgical clipping. Over the last 2 decades, endovascular treatment technology has evolved immensely, which is likely another contributing factor to the treatment approach bias, and consequently the issue of generalizability. These 2 issues curtail the generalizability of the results of this meta-analysis, because it essentially focused on a treatment modality that is becoming less commonly applied in practice.

Importantly, evidence supports favorable functional outcome following coiling compared with surgical clipping treatment, though this pattern is biased toward good-grade aSAH patients with small, anterior circulation aneurysms. This might suggest that the posttreatment executive function impairments, though insignificant, were overestimated in this meta-analysis due to the biased patient population. A separate analysis excluding coiled UIA patients was performed for the domains of executive function and verbal memory. Results of these analyses were similar to those that included these patients.

Lastly, a methodological issue observed in the included studies relates to the lack of consistent exclusion criteria for preexisting cognitive impairments. While 4 of the studies explicitly state that cognitively impaired patients at baseline were excluded, the other 3 make no such claims. While this could represent a simpler problem with incomprehensive manuscript preparation, it nevertheless introduces uncertainty into their results. Future studies of the effect of UIA treatment on cognition should have the following features: a large sample size with sufficient power to detect differences in cognition before and after treatment and a battery of tests that evaluate major cogni-

<table>
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<th>Table 2. Individual unweighted study effect sizes</th>
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<td>Domain &amp; Study</td>
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<tr>
<td>Executive functions</td>
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<tr>
<td>Haug et al., 2009</td>
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<tr>
<td>Preiss et al., 2012 (clipped &amp; coiled)</td>
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<tr>
<td>Preiss et al., 2012 (clipped only)</td>
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<tr>
<td>Tuffiash et al., 2003</td>
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<tr>
<td>Hillis et al., 2000</td>
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<tr>
<td>Verbal memory (both)</td>
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<tr>
<td>Haug et al., 2009</td>
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<tr>
<td>Preiss et al., 2012 (clipped &amp; coiled)</td>
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<td>Preiss et al., 2012 (clipped only)</td>
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<tr>
<td>Hillis et al., 2000</td>
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<tr>
<td>Visual memory</td>
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<td>Tuffiash et al., 2003</td>
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<td>Kubo et al., 2010</td>
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<td>Visuospatial functions</td>
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<td>Tuffiash et al., 2003</td>
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<tr>
<td>Fukunaga et al., 1999</td>
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<td>Pereira-Filho et al., 2010</td>
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FIG. 3. Funnel plot indicating the distribution of the effect sizes for executive functions (A), visuospatial functions (B), and global cognitive functions (C); the log of the effect sizes versus the standard error.
and visual (lower) memory; the log of the effect sizes versus the standard error.

Conclusions

This meta-analysis found trends toward treatment-mediated changes in executive functions and visual and verbal memory, though the low number of studies and biased treatment modalities prevents any strong conclusions. Nevertheless, this study highlights the importance of establishing the cognitive profile of patients both prior to and after treatment to advise future treatment and rehabilitation approaches. Studies with larger sample sizes and a greater variety of neuropsychological tests are required to determine whether treatment of UIAs affects cognitive functions. Additionally, brain imaging such as MRI could provide greater clarity on whether aneurysm location and other diseases that may be associated (e.g., white matter lesions) have an effect on cognitive outcome.

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References


Disclosure
Dr. Macdonald reports that he has direct stock ownership in Edge Therapeutics, Inc.

Author Contributions
Conception and design: Bonares. Acquisition of data: Bonares, Egeto, Veselý. Analysis and interpretation of data: Bonares, Egeto. Drafting the article: Bonares, Egeto, Veselý. Reviewed submitted version of manuscript: all authors. Statistical analysis: Bonares, Egeto. Conception and design: Bonares. Acquisition of data: Bonares, Egeto, Veselý. Analysis and interpretation of data: Bonares, Egeto. Drafting the article: Bonares, Egeto. Reviewed submitted version of manuscript: all authors. Statistical analysis: Bonares, Egeto. Conception and design: Bonares. Acquisition of data: Bonares, Egeto, Veselý. Analysis and interpretation of data: Bonares, Egeto. Drafting the article: Bonares, Egeto. Reviewed submitted version of manuscript: all authors. Statistical analysis: Bonares, Egeto. Conception and design: Bonares. Acquisition of data: Bonares, Egeto, Veselý. Analysis and interpretation of data: Bonares, Egeto. Drafting the article: Bonares, Egeto. Reviewed submitted version of manuscript: all authors. Statistical analysis: Bonares, Egeto.

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