Cognitive Neuropsychology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/pcgn20

Sex differences in the effects on the brain of early cognitive stimulation

Saul Sternberg

To cite this article: Saul Sternberg (2021): Sex differences in the effects on the brain of early cognitive stimulation, Cognitive Neuropsychology, DOI: 10.1080/02643294.2021.2004108

To link to this article: https://doi.org/10.1080/02643294.2021.2004108

Published online: 28 Nov 2021.

COGNITIVE NEUROPSYCHOLOGY
https://doi.org/10.1080/02643294.2021.2004108

Sex differences in the effects on the brain of early cognitive stimulation*

Saul Sternberg

Psychology, University of Pennsylvania, Philadelphia, PA, USA

ABSTRACT
A study by Farah and colleagues (2021) of the effects on the adult brain of a cognitively intense early childhood experience revealed large effects, but primarily in the brains of male subjects, while causing equally large increases of childhood IQ in males and females. The present analysis advances and tests a conjecture about one reason for the sex difference. Among the control subjects, the summed volume of four small regions of the cortex, associated with language and cognitive processes, is proportionally larger in females. Based on these four regions, a new brain measure, the "cognitive ratio", is defined. The cognitive ratio is found to be strongly and negatively correlated with variations in the effect of the early experience on brain volume among the males, and explains a large proportion of the difference between males and females, as well as the greater sensitivity of the male brains to that experience.

ARTICLE HISTORY
Received 8 June 2021
Revised 7 October 2021
Accepted 1 November 2021

1. Background

Farah and colleagues (2021) reported the effects on the adult brain of a cognitively challenging early childhood intervention applied for five years, starting in infancy, to children from low-socioeconomic African-American families: the Abecedarian Project (Ramey, 2018; Ramey et al., 1976). From infancy through age five years, members of the randomly selected intervention group experienced high levels of individually paced cognitive and language experiences. As described by Farah et al. (2021), "The programme utilized the Learning Games curriculum (Sparling & Lewis, 1984), which is based on the Vygotskian view of the centrality of language in cognitive development — that children learn self-regulation by internalizing speech. Infant activities included talking to the child, playing with cause-and-effect toys or picture books, and offering infants an opportunity to react to sights and sounds in the environment. As children grew, the curriculum shifted toward more conceptual and skill-based learning games and interactions, always using language, even in motor skill activities, and eliciting language from the child." Members of both the intervention and matched control groups were provided with nutritional supplementation and access to healthcare.

Partly because the brains of only 60% of the subjects in the original study were scanned (in their early forties), sample sizes are limited: 29 of the scanned subjects were in the randomly sampled subgroup who had experienced the intervention (15 males and 14 females); while 18 of the scanned subjects had experienced the control condition (9 males and 9 females). Normally the small size of these samples would discourage fine-grained exploration of the data. However, as discussed in Farah et al. (2021), the study had adequate power for detecting a large effect on brain volume, and the expected and obtained main effects are both large. Furthermore, given the uniqueness of this study[1], the data are especially valuable, and invite us to learn as much as possible from them. (Partly for this reason, some details of the data, not reported in Farah et al. (2021), are provided in the appendices of the present paper.) Finally, as we shall see, the effects to be revealed are sufficiently large and systematic so that persuasive conclusions emerge, despite the limited sample sizes. (It can be argued that the strength of the evidence implied by small *p*-values, such as many of those reported below, is actually greater when sample sizes are small; Demidenko, 2016; Royall, 1986.)

CONTACT Saul Sternberg saul@upenn.edu Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA
*The analyses on which this report is based were conducted in R (R Core Team, 2019).
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Table 1. Age Four Mean IQ.

Group	Control	(N)	Intervention	(N)	Difference	SE(Difference)
Male	87.6	(9)	101.2	(14*)	+13.6	4.8
Female	87.6	(8*)	99.7	(14)	+12.1	4.6

Note: The Stanford-Binet intelligence test (Form L-M) was used, administered by staff blind to group assignment. IQ data for two of the subjects (one female control subject and one male intervention subject) are missing; hence the starred values of N.

2. Intervention effects on males and females

Some of the basic means data from the study, relevant to the present analyses, are provided in Appendix A.[2] Perhaps the most remarkable aspect of the outcomes of the early intervention are the sex differences in its effects on brain morphology, especially when taken together with the absence of such a difference in its effects on an important behavioural measure, the IQ tested at age four. The existence of sex differences in brain structure is well known (e.g., Blanton et al., 2004; Cosgrove et al., 2007; Lotze et al., 2019; Liu et al., 2020; Wierenga, L. M., et al., 2020). However, here we have a sex difference in the sensitivity of that structure to childhood experience. Evidence from animals (Juraska, 1986) tends to favour greater brain plasticity among males. Possible synaptic mechanisms for sex differences in brain plasticity among humans have been considered (e.g., Dachtler & Fox, 2017). And Mottron et al. (2015) have argued that the sex difference in autism frequency results from greater brain plasticity among males. However, as we shall see, much of the sex difference reported in Tables 2 and 3 can be explained without appealing to a general sex difference in brain plasticity.

Mean IQs for the four groups of scanned subjects are shown in Table 1. The difference between the effects of the intervention on male and female IQ, 1.4 points (SE=6.6), is negligible, while an ANOVA (Appendix B) shows the effect on the combined groups to be highly significant ($P_F = 0.0003$; $P_{perm} = 0.0006$).[3] In contrast, the patterns revealed by most of the brain volume measurements differ dramatically between males and females. Table 2 shows the results for the volume of the whole brain, and Table 3 for the volume of the cortex. (See Appendix C and D for ANOVAs.) One way to describe the contrast is that females achieved the same increase in IQ as males, but did so with a radically smaller increase in brain volume.[4]

Table 2. Mean Brain Volume (cc).

Group	Control	Intervention	Difference	SE(Difference)
Male	938.1	1030.9	+92.8	25.3
Female	868.5	870.0	+1.5	31.5

Table 3. Mean Cortex Volume (cc).

Group	Control	Intervention	Difference	SE(Difference)
Male	433.8	480.3	+46.6	12.1
Female	400.8	402.1	+1.3	14.2

3. Why the sex difference? A conjecture

Why were the brains of the female subjects influenced so much less by the intervention than those of the male subjects? Sex differences found in the brains of the control subjects provide a hint. The data revealed a difference related to the four cortical regions that had been selected a priori as regions of interest by Farah et al. (2021) — ROIs that were selected because of their relevance to language and cognitive processes: the bilateral anterior cingulate gyrus, left superior temporal gyrus, and left and right inferior frontal gyrus. Despite the fact that the mean cortex volume for control females was about 8% smaller than for control males, the mean summed volume of these four regions was actually 2% *greater:* 19.0 cc. versus 18.6 cc (Appendix A). Let us denote the proportion of cortex occupied by these four regions — the summed volume of these four regions as a percentage of the volume of the cortex — the "cognitive ratio". Among the control subjects, the mean cognitive ratio was larger in females, for whom it was 4.75%, on average, compared to 4.29% in males. The mean difference (0.46%) is highly significant (see Table 5), with a *p*-value of 0.002, and a 95% confidence interval of (0.17%, 0.76%), based on BCa bootstrap calculations.[5]

Table 4. Mean Cognitive Ratio.

Group	Male	Female	Difference	SE(Difference)
Control	4.29%	4.75%	0.46%	0.16%
Intervention	4.61%	4.95%	0.33%	0.16%

Table 5. ANOVA of Cognitive Ratio.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	0.7796	5.42	0.025	0.018
Sex	1	1.6652	11.58	0.0015	0.0014
Intervention x Sex	1	0.0454	0.32	0.58	0.44
Residuals	43	0.1438			

As shown in Tables 4 and 5, and Figure 1, the female cognitive-ratio advantage characterizes the intervention subjects as well, despite the fact that the cognitive ratio was increased by the intervention and that the effect of the intervention on male brain volume was dramatically greater.

One plausible mechanism that explains the intervention effect and the sex difference in its magnitude depends on three assumptions. Assumption 1: Individual differences in cognitive ratio measured in midlife reflect corresponding differences in the young brain; Assumption 2: The intervention is more challenging when the cognitive ratio is smaller; and Assumption 3: A greater cognitive challenge in childhood leads to a greater increase in brain volume. Independent support is currently available only for Assumption 3, and derives from the effects on the brain of the intervention compared to the less cognitively challenging control condition, reported by Farah et al. (2021).

Individual values of cognitive ratio and brain volume are provided in Appendix F.

4. A test of the conjecture

How might we test the possibility that differences in cognitive ratio modulate the effects of the intervention on brain volume? Suppose that a larger cognitive ratio is associated with smaller effects of the early intervention on the brain, as suggested by the sex differences described above. Then we should see such a relationship among the male subjects who experienced the intervention (and whose brains are substantially different from those of the controls, on average, as a consequence). For those fifteen male subjects, let us consider whether, within that group, there are negative correlations between the cognitive ratio and three other measures: the volume of the

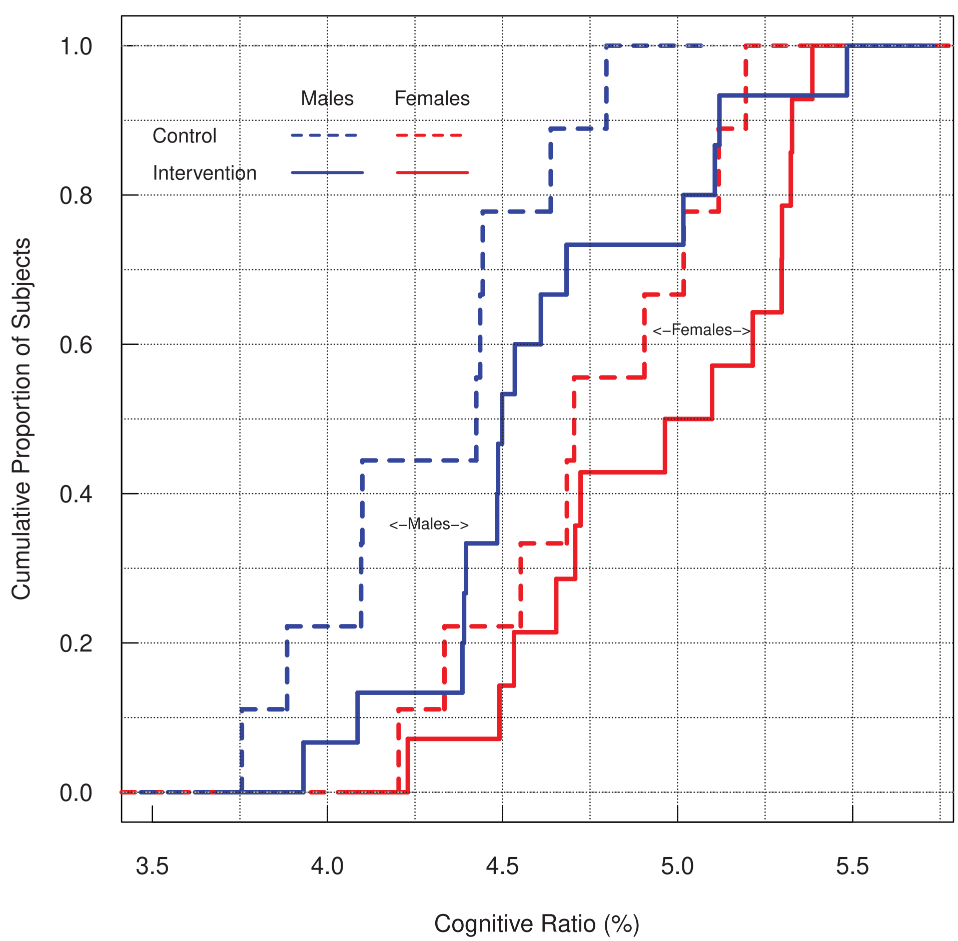

Figure 1. Distributions of cognitive ratio for four groups of subjects.

Table 6. Correlations of Cognitive Ratio with Three Measures of Brain Volume for Fifteen Male Intervention Subjects.

Correlation Type	Percentage Bend		Pearson			Slope
Region	Correlation	*P*-value	Correlation	*P*-value	95% Interval	(cc/percent)
Whole Brain	−0.61	0.015	−0.59	0.014	(−0.82, −0.14)	−113.7 ± 29.8
Cortex	−0.58	0.022	−0.52	0.006	(−0.77, −0.20)	−42.6 ± 9.3
Remaining Brain	−0.55	0.036	−0.57	0.078	(−0.85, +0.09)	−7.7 ± 28.5

Note: The percentage bend correlation calculations used the R package WRS (Wilcox & Schonbrodt, 2019); the Pearson correlation calculations used the R package mcr (Manuilova et al., 2014). Slope values are based on BCa bootstrap calculations.

whole brain, the volume of the cortex, and the volume of the brain excluding the cortex ("remaining brain"). (For those subjects, the means of the increases in these volume measures caused by the early intervention are remarkably large: 9.9%, 10.7%, and 9.2%, respectively, as shown in Table A2.[6]) The correlations of these three volume measures with cognitive ratio are shown in Table 6; they are indeed negative and substantial.

Unlike the Pearson correlation coefficient, the percentage bend correlation coefficient (Wilcox, 1994; 2017) is robust — less sensitive to violations of normality. Nonetheless, the values of the two correlation coefficients, and the corresponding *p*-values for tests of independence, are in good agreement. Also shown are the slopes of fitted linear functions, relating brain volume to cognitive ratio, and their standard errors, as estimated by a robust regression method.[7] The *p*-values associated with the three linear functions are 0.0022, 0.0005, and 0.0260, respectively.[8]

A possible concern is that the negative correlation between cognitive ratio and remaining brain volume (for example) is an artefact, resulting from the cognitive ratio denominator (cortex volume) being positively correlated with remaining brain volume (Pearson r = + 0. 71, among intervention males). However, for the three other groups, within which cognitive ratio and remaining brain volume both vary (as shown in Figure 2C), the correlations between cortex and remaining brain volumes are also high and positive: r = + 0. 58 for control males, r = + 0. 54 for intervention females, and r = + 0. 77 for control females. Yet, as will be seen in Section 5, the correlation in these other groups between cognitive ratio and remaining brain volume is negligible.

As detailed in Appendix E, the volume of each of the four regions used to determine the cognitive ratio, expressed as a percentage of cortex volume, shares the properties of their summed volume expressed that way: For all of them, remarkably, the female percentage is greater than the male percentage for both control and intervention groups, and, among male intervention subjects, also remarkably, all of them are correlated negatively with the volumes of brain, cortex, and remaining brain. That these properties are shared justifies combining their volumes, and working with their sum

Panel A of Figure 2 shows the relation between cognitive ratio and brain volume for the male intervention subjects. A linear function was chosen because it provides the simplest description of the relationship, not because we have reason to believe that the true relationship is linear; we shall see in Section 7 that it may not be. Assuming linearity, note the considerable magnitude of the effect, as indicated by the slope (−113.4 cc/percent; 95% confidence interval = (−205,−32)) of the solid line:[9] An increase in the cognitive ratio from 4.0% to 5.5% (an increase of only 1.5% of cortex volume) is associated with a decrease in brain volume of about 171 cc, or about 17%. One consequence of the intervention on male brains is the great increase in individual variability in brain volume: the 20% winsorized variance of brain volumes for the male intervention group is 3256 cc^4, compared to 920 cc^4 for the male control group, a ratio of 3.54 ($p = 0.034$).[10]

5. Rejection of a competing hypothesis

The relationships shown in Table 6 and Figure 2A between the cognitive ratio and other brain volume measures characterize the brains of fifteen adults who experienced the intensive early cognitive intervention and whose brains changed radically as a consequence. Do these correlations depend on the substantial effects of the intervention on brain volume in this group of subjects, or are they a general property of brains? To answer this question let us consider whether the relationship between the cognitive ratio and other volume measures

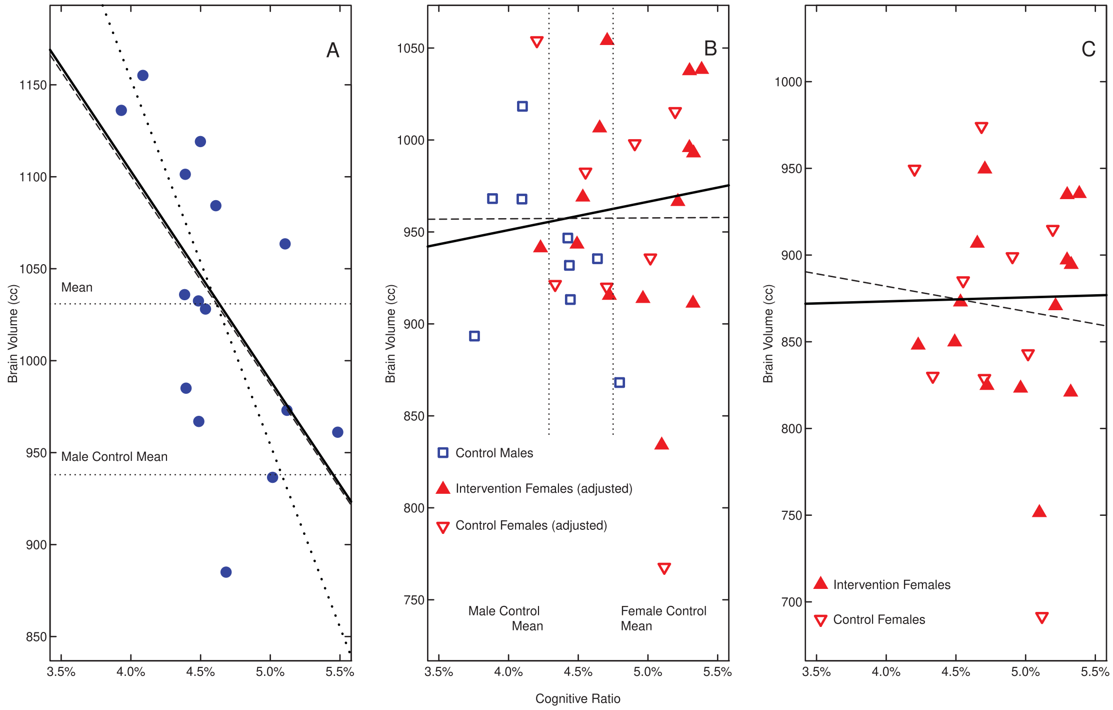

Figure 2. Relation between cognitive ratio and brain volume for three sets of subjects. In each case, the heavy unbroken line was fitted using the function lmrob in the R package robustbase (Maechler et al., 2021), a robust method suitable for small samples (Koller & Stahel, 2011), and the lighter broken line was fitted using ordinary least squares. Note the differences among the three ordinate scales. (A): Relation between cognitive ratio and brain volume for fifteen male intervention subjects. Broken and heavy solid lines have slopes of −113.4 cc/percent and −113.7 cc/percent, respectively. The dotted line describes the relation required to explain the difference between the effects of the intervention on male and female brain volume solely in terms of the mean cognitive-ratio difference between males and females. (B): Relation between cognitive ratio and brain volume for three groups of subjects combined: control males, control females, and intervention females. Brain volumes for the latter two groups have been multiplied by 1.11 to eliminate the systematic difference between male and female brain volume. Broken and heavy solid lines have slopes of +0.5 cc/percent and +15.4 ± 28.3 cc/percent, respectively. The vertical dotted lines indicate mean values of the cognitive ratio for control males and females. (C): Relation between cognitive ratio and brain volume for two groups of subjects combined: control females, and intervention females. Broken and heavy solid lines have slopes of −14.5 cc/percent and +2.3 ± 39.2 cc/percent, respectively. Because no male data are included, female brain volumes have not been adjusted.

obtains for the control subjects (nine males and nine females, who did not experience the cognitive intervention), and the fourteen females who experienced the intervention, but whose brain volume changed minimally as a result. To combine the data from these three groups, and avoid spurious effects of the systematic difference between male and female brain volume, this difference was removed by adjusting the female volumes: multiplying them by an estimate (1.11) of the ratio of mean volumes of the brains of males and females.[11]

Table 7. Correlations of Cognitive Ratio with Three Measures of Brain Volume for Thirty- Two Remaining Subjects, Using Adjusted Volumes for Females.

Correlation Type	Percent Bend		Pearson		
Region	Correlation	P-value	Correlation	P-value	95% Interval
Whole Brain	−0.03	0.87	−0.11	0.55	(−0.42, +0.25)
Cortex	−0.11	0.54	−0.14	0.44	(−0.46, +0.23)
Remaining Brain	−0.04	0.85	−0.06	0.72	(−0.42, +0.30)

The results in Table 7 show that the correlation is negligible, which is also indicated by the flatness of the fitted lines in Figure 2B. Note the ordinate scale difference between Panels A and B, a result of the brains of the intervention males being larger than those of the other subjects, even after adjusting the female volume for the sex difference.

That combining the male control data with adjusted values for the volume of female brains does not lead to a distorted impression of the correlations is shown by the results in Table 8, for just the female subjects, which are consistent with the values in Table 7. This is also shown by Figure 2C, in which brain volume of just the control and

Table 8. Correlations of Cognitive Ratio with Three Measures of Brain Volume for Twenty-three Female Subjects.

Correlation Type	Percent Bend		Pearson		
Region	Correlation	P-value	Correlation	P-value	95% Interval
Whole Brain	+0.05	0.81	−0.08	0.65	(−0.43, +0.30)
Cortex	−0.09	0.67	−0.14	0.48	(−0.49, +0.26)
Remaining Brain	+0.03	0.87	−0.03	0.87	(−0.43, +0.37)

intervention females is plotted against the cognitive ratio, for results very similar to those shown in Figure 2B.

How persuaded should we be by the correlation differences between the male intervention subjects and the others? For brain volume, tests of the significance of the difference between the Pearson correlations in Tables 6 and 7 using Fisher's z-transform method yields a *p*-value of $p=0.097$, while tests of the significance of the difference between the percentage bend correlations yields a *p*-value of $p=0.063$. Corresponding *p*-values when the comparison is between Table 6 and Table 8 are $p=0.104$ and $p=0.040$.[12]

What is evident, then, is that the striking correlation between cognitive ratio and brain volume is limited to those subjects in a group with both of two characteristics: They experienced the early intervention *and* their brains changed substantially as a result.[13]

6. How much does the cognitive ratio explain?

The possibility that differences in the cognitive ratio may explain only a part of the sex differences in the effects of the intervention on the brain is evident when we consider the difference between the mean cognitive ratios for male and female control subjects (4.29% versus 4.75%, for a difference of 0.46%, Table 4) together with the estimated slope of the relationship shown in Figure 2A (−113.7 cc/percent). Together, these values lead us to expect a difference between the effects of the intervention on male and female brain volume of 52.3 cc; the observed difference of 92.8 cc (Table 2) is substantially greater. For the difference in cognitive ratio to explain the full difference between the effects on male and female brain volume, rather than only 56% of the difference, the slope of the line that represents the relationship would have to be greater by a factor of 92.8/52.3, or 1.77. A dotted line with the required slope (−201.3 cc/percent) is shown in Figure 2A.[14] However, given the small size of our sample and the resulting estimation error, we cannot exclude the possibility that the true relationship is the one described by the dotted line. Indeed, the slope of this line falls within the 95% confidence interval for the estimated slope of the best-fitting line (−205, −32 cc/percent).

That the association between a smaller cognitive ratio and a larger intervention effect on the brain is not found in the brains of the male control subjects seems puzzling at first: Their early experience also presumably influenced brain development. Why wasn't their susceptibility to the effects of this experience on brain volume modulated by the cognitive ratio? One possibility: It is because their early experience was less cognitively challenging than the experience of the intervention subjects.

Some of the ancillary findings related to the brains of the male intervention subjects and to the cognitive ratio are documented in Appendix G. The correlation patterns shown there for the cognitive ratio and for its numerator (the summed volume of four regions, "sum4") differ greatly, suggesting that the cognitive ratio and the summed volumes (its numerator) reflect different aspects of brain function.

7. Nonlinear relation between cognitive ratio and post-intervention brain volume

If the relation between cognitive ratio and brain volume among intervention subjects were actually linear, then we would expect these variables to be correlated among the female intervention subjects. Yet Figure 2C suggests that there is no such correlation; this is confirmed by the fact that the slope (+2. 8 ± 3. 2 cc/percent) of a linear function relating brain volume to cognitive ratio for just the intervention females cannot be distinguished from zero. As a rough measure of the magnitude of the relation between cognitive ratio and brain volume, the slope of a linear function is useful. However, as well as can be determined given our limited sample sizes, the actual function is, in fact, not linear: For subjects with cognitive ratios above 4.6%, the correlation appears to be absent. This is shown by examining the relation for the combined group of 29 intervention subjects.[15] For the 12 intervention subjects with cognitive ratios less than 4.6% (which includes 60% of the intervention males, but only 21% of the intervention females), the estimated slope of a linear function is -225.4 cc/percent (about twice the slope described in Section 4 for all the intervention males), whereas for the 17 subjects with values greater than 4.6% (which includes 79% of the intervention females and 40% of the intervention males), the estimated slope is -2.4 cc/percent. (Given the sample sizes, it is not surprising that the standard errors of these slope estimates are large: 76.1 and 70.5 cc/percent, respectively.)[16] Let us assume that the true relation between cognitive ratio and brain volume is nonlinear and decelerating, as suggested by these results, and can be approximated by the two-part broken-line regression function described above.

There are two implications. First, because most of the intervention females have high values of the cognitive ratio, which places them on the relatively flat part of the function, we can understand the absence of a correlation between cognitive ratio and brain volume for this group. Second, we can again ask how much of the sex difference in the effect of the intervention on brain volume can be explained, now assuming the broken-line function rather than a linear function. Given that function and the observed values of cognitive ratio, the mean fitted intervention effects for males and females are 75.5 and 22.3 cc, respectively; the difference, 52.2 cc is again substantially smaller than the observed difference, only 58.4% of that difference. Because of the small sample sizes and resulting large SEs of these estimates, the findings that sex differences in cognitive ratio cannot fully explain the sex differences in the intervention effect should be taken as only suggestive. However, they leave open the possibility that there is another contributor, one possibility being a sex difference in brain plasticity (Juraska, 1986; Mottron et al., 2015).

8. Summary and conclusions

A prolonged cognitively intense early intervention, while producing equal IQ increases in male and female children, produced much greater increases in adult brain volume in males. (Future studies of this kind should of course incorporate early brain measurements.)

Among these subjects, the volumes of four cortex regions associated with cognitive processes (bilateral anterior cingulate gyrus, left superior temporal gryrus, right inferior frontal gyrus, and left inferior frontal gyrus), expressed as a proportion of cortex volume, are greater in adult females than males; I call the summed volume of these four regions as a percentage of cortex volume the “cognitive ratio”. (It would, of course, be extremely interesting to know the extent to which the sex difference in cognitive ratio in these subjects generalizes to others.)

To test whether the difference in cognitive ratio could be one reason for the sex difference in the effects of the intervention, I looked at the relationship between cognitive ratio and brain volume among the male subjects who had experienced the intervention. I discovered that within that group there is a substantial negative correlation between the cognitive ratio and brain volume.

This suggests two possibilities.

A. The increase in brain volume due to the intervention is negatively related to cognitive ratio, or, alternatively,
B. There is a general negative relationship between brain volume and cognitive ratio.

By testing for the negative relationship among female intervention subjects (whose mean brain volume had been increased minimally by the intervention) together with male and female control subjects, I ruled out possibility B, leaving possibility A (Table 7, Figure 2B). This conclusion was strengthened by examining just the female intervention and control subjects (Table 8, Figure 2C).

We can conclude that one contributor to the sex difference in the effect of the intervention on brain volume is the sex difference in cognitive ratio. However, as noted in Sections 6 and 7, the data suggest that this may not be the only contributor.

The ratio of the volumes that define the cognitive ratio to cortex volume appears to reflect different aspects of brain function from the volumes themselves.

Limitations of this study include the absence of brain measurements early in life, and the small sample sizes.

Notes

1. The brains of no other human beings subjected to a sustained randomized manipulation of early cognitive stimulation have been measured.
2. Many of the values in these tables also appear in Tables 3 and 4 of Farah et al. (2021), in which details of the brain imaging methods can also be found.
3. Throughout this paper, P_F is from a conventional ANOVA associated with an F-test; P_{perm} is from a corresponding permutation test, computed with the R-package lmPerm (Wheeler & Torchiano, 2016). More generally, wherever feasible in this paper, both conventional and nonparametric statistical tests and estimates are used, to reduce the chance of misleading conclusions that might result from the sample sizes being small.
4. It should be kept in mind that IQ was measured at age four, whereas brains were scanned about four decades later. The present analysis depends on assuming that time and experience during the four intervening decades did not selectively reduce the effects of the intervention on female brains, or selectively increase its effects on male brains.
5. These calculations used the R package wBoot (Weiss, 2016).
6. These three measures are, of course, not independent: the second and third regions are contained within and, together, constitute the first.
7. The method used is the function lmrob, in the R package "robustbase: Basic Robust Statistics" (Maechler et al., 2021), suitable for use with small samples (Koller & Stahel, 2011)
8. If the relation between the cognitive ratio and brain volumes were equally strong for all regions of the brain, then we would expect slope(cortex) as a proportion of slope(brain) to equal the mean value of volume(cortex) as a proportion of volume(brain). The former proportion is 0.375 while the latter is 0.466, which suggests that the relation to the cognitive ratio is weaker for the cortex than for the remaining brain. However, although the sign of the estimated slope difference (the slope of a linear function relating the difference between remaining brain volume and cortex volume to the cognitive ratio, −30. 3 ± 31. 7) is consistent with the suggestion, its SE is too great for us to draw this conclusion.
9. The 95% confidence interval is based on BCa bootstrap calculations implemented with the R package mcr (Manuilova et al., 2014). The estimated zero-intercept of the fitted line is 1558 cc.
10. It is also noteworthy that the winsorized brain-volume variance of the pooled male groups (3586 cc^4) is about twice as great as the winsorized variance for the pooled female groups (1872 cc^4), consistent with the general finding of greater variance for male brains (Wierenga, et al., 2020).
11. For the control groups in our sample, these ratios, are 1.080, 1.082, and 1.078 for brain, cortex, and the difference ("remaining brain"), respectively. However, because of the small sample size and the range of volumes, this ratio is highly uncertain: A BCa bootstrap 95% confidence interval for the ratio is (1.02, 1.18). Among "normal subjects of European ancestry", Cosgrove et al. (2007, page 848) report a male-female ratio of 1.11, while Allen et al. (2002, Table 1) report a ratio of 1.13 for the same population. The ratio based on measurements of large samples of UK residents by Ritchie et al. (2018, Table 1) is 1.11. In what follows 1.11 will be used, but none of the conclusions changes when 1.08 is used, instead.
12. These tests used the cocor function in the R package cocor (Diedenhofen & Musch, 2015) and the twocor function in the R package WRS (Wilcox & Schonbrodt, 2019), respectively.
13. It is also true, of course, that these subjects were all males. If the data set were larger, and included some females whose brain volumes were increased substantially by the intervention, it might be possible to distinguish whether the correlation depends on having a brain whose volume increased because of the intervention, or on being male.
14. If the effect of the intervention on brain volume is assumed to be proportional to brain volume, then the line expressing the relation between cognitive ratio and brain volume for females would be about 11% less steep, the expected difference between effects smaller than 52cc, and the disparity between observed and expected effects even greater.
15. For this purpose, female brain volumes were multiplied by 1.11. (see note 11.).
16. These values were determined using the function lmrob, in the R package "Robust base : Basic Robust statistics" (Maechler et al. 2021). The corresponding slope estimates determined by ordinary least squares are −132.0 and −11.2 cc/percent, respectively.

Acknowledgements

I am grateful to Martha J. Farah for interesting me in the work that led to Farah et al. (2021) and for her comments on the present manuscript, to C. T. Ramey and S. L. Ramey for permitting use of the data, to Vincent Hurtubise and Mark Davidson for computer-system support, and to John Kounios, and especially Allen Osman and Bradford Mahon, the action editor, for comments on the manuscript. The subjects are among those who participated in the Abecedarian Project; see Farah et al. (2021) for information about the subset of subjects whose brains were scanned. Investigation of the brains of these subjects was organized by P. R. Montague and M. J. Farah and aided by L. Bateman and L. Sonnier. Images were acquired by P. R. Montague, and processed by J. T. Duda, M. J. Farah, T. Lohrenz, and T. A. Nichols.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Supported by the William N. Sternberg Research Fund for Human Information Processing.

ORCID

Saul Sternberg http://orcid.org/0000-0002-5783-6285

References

Allen, J. S., Damasio, H., & Grabowski, T. J. (2002). Normal neuroanatomical variation in the human brain: An MRI-volumetric study. *American Journal of Physical Anthropology*, *118*(4), 341–358. https://doi.org/10.1002/ajpa.10092

Blanton, R. E., Levitt, J. G., Peterson, J. R., Fadale, D., Sporty, M. L., Lee, M., To, D., Mormino, E. C., Thompson, P. M., McCracken, J. T., & Toga, A. W. (2004). Gender differences in the left inferior frontal gyrus in normal children. *NeuroImage*, *22*(2), 626–636. https://doi.org/10.1016/j.neuroimage.2004.01.010

Cosgrove, K. P., Mazure, C. M., & Staley, J. K. (2007). Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biological Psychiatry*, *62*(8), 847–855. https://doi.org/10.1016/j.biopsych.2007.03.001

Dachtler, J. D., & Fox, K. (2017). Do cortical plasticity mechanisms differ between males and females? *Journal of Neuroscience Research*, *95*(1-2), 518–526. https://doi.org/10.1002/jnr.23850

Demidenko, E. (2016). The *p*-value you can't buy. *The American Statistician*, *70*(1), 33–38. https://doi.org/10.1080/00031305.2015.1069760

Diedenhofen, B., & Musch, J. (2015). Cocor: A comprehensive solution for the statistical comparison of correlations. *PLoS ONE*, *10*(4): https://doi.org/10.1371/journal.pone.0121945.

Farah, M. J., Sternberg, S., Nichols, T. A., Duda, J. T., Lohrenz, T., Luo, Y., Sonnier, L., Ramey, S. L., Montague, R., & Ramey, C. T. (2021). Randomized manipulation of early cognitive experience impacts adult brain structure. *Journal of Cognitive Neuroscience*, *33*(6), 1197–1209. https://doi.org/10.1162/jocn_a_01709

Juraska, J. M. (1986). Sex differences in developmental plasticity of behavior and the brain. In W. T. Greenough, & J. M. Juraska (Eds.), *Developmental neuropsychobiology* (pp. 409–422). Academic Press.

Koller, M., & Stahel, W. A. (2011). Sharpening Wald-type inference in robust regression for small samples. *Computational Statistics and Data Analysis*, *55*(8), 2504–2515. https://doi.org/10.1016/j.csda.2011.02.014

Liu, S., Seidlitz, J., Blumenthal, J. D., Clasen, L. S., & Raznahan, A. (2020). Integrative structural, functional, and transcriptomic analyses of sex-biased brain organization in humans. *Proceedings of the National Academy of Sciences*, https://doi.org/10.1073/pnas.1919091117

Lotze, M., Domin, M., Gerlach, F. H., Gaser, C., Lueders, E., Schmidt, C. O., & Neumann, N. (2019). Novel findings from 2,838 adult brains on sex differences in gray matter brain volume. *Scientific Reports*, *9*(1), 1671. https://doi.org/10.1038/s41598-018-38239-2

Maechler, M., Rousseeuw, P., Croux, C., Todorov, V., Ruckstuhl, A., Salibian-Barrera, M., Verbeke, T., Koller, M., Conceicao, E. L., & di Palma, M. A. (2021). *robustbase: Basic Robust Statistics*. R package version 0.93-8.

Manuilova, E., Schuetzenmeister, A., & Model, F. (2014). mcr: Method comparison regression. R package version 1.2.1. https://CRAN.R-project.org/package=mcr

Mottron, L., Duret, P., Mueller, S., Moore, R. D., Forgeot d'Arc, B., Jacquemont, S., & Xiong, L. (2015). Sex differences in brain plasticity: A new hypothesis for sex ratio bias in autism. *Molecular Autism*, *6*(1), 33. https://doi.org/10.1186/s13229-015-0024-1

Ramey, C. T. (2018). The abecedarian approach to social, educational, and health disparities. *Clinical Child and Family Psychology Review*, *21*(4), 527–544. https://doi.org/10.1007/s10567-018-0260-y

Ramey, C. T., Collier, A., Sparling, J. J., Loda, F. A., Campbell, F. A., Ingram, D. L., & Finkelstein, N. W. (1976). The Carolina abecedarian project: A longitudinal and multidisciplinary approach to the prevention of developmental retardation. In T. D. Tjossem (Ed.), *Intervention strategies for high risk infants and young children* (pp. 629–665). University Park Press.

R Core Team. (2019). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. URL https://www.R-project.org/

Ritchie, S. J., Cox, S. R., Shen, X., Lombardo, M. V., Reus, L. M., Alloza, C., Harris, M. A., Alderson, H. L., Hunter, S., Neilson, E., & Liewald, D. C. (2018). Sex differences in the adult human brain: Evidence from 5216 UK biobank participants. *Cerebral Cortex*, *28*(8), 2959–2975. https://doi.org/10.1093/cercor/bhy109

Royall, R. M. (1986). The effect of sample size on the meaning of significance tests. *The American Statistician*, *40:4*, 313–315. DOI:10.1080/00031305.1986.10475424.

Sparling, J., & Lewis, I. (1984). *Learning Games for threes and fours: A guide to adult/child play*. Berkley Books. https://doi.org/10.1007/BF01617063.

Weiss, N. A. (2016). wBoot: Bootstrap Methods. R package version 1.0.3. https://CRAN.R-project.org/package = wBoot

Wheeler, B., & Torchiano, M. (2016). lmPerm: Permutation tests for linear models. R package version 2.1.0. https://CRAN.R-project.org/package=lmPerm

Wilcox, R. R. (1994). The percentage bend correlation coefficient. *Psychometrika*, *59*(4), 601–616. https://doi-org.proxy.library.upenn.edu/10.1007/BF02294395 https://doi.org/10.1007/BF02294395

Wilcox, R. R. (2017). *Introduction to robust estimation and hypothesis testing* (4th Edition). Elsevier.

Wilcox, R. R., & Schonbrodt, F. D. (2019). The WRS package for robust statistics in R (version 0.36). https://github.com/nicebread/WRS

Appendix A: Brain Region Volumes

Table A1. Females: Means and (Standard Errors) of Brain Region Volumes for Control and Intervention Groups.

Group	Control (N=9)		Intervention (N=14)		Difference	
Volume in cc of:						
Brain	868.53	(27.91)	870.00	(14.66)	0.17%	(1.69%)
Cortex	400.77	(12.57)	402.09	(6.56)	0.33%	(1.64%)
**AntCingGyrus*	5.40	(0.11)	5.47	(0.28)	1.29%	(5.12%)
**LeftSupTempGyrus*	4.57	(0.30)	4.41	(0.13)	−3.40%	(2.84%)
**RightInfFrontGyrus*	4.52	(0.16)	4.91	(0.19)	8.61%	(4.22%)
**LeftInfFrontGyrus*	4.47	(0.17)	5.11	(0.17)	14.24%	(3.88%)
Remaining Cortex	381.81	(12.21)	382.19	(6.18)	0.10%	(3.58%)
Remaining Brain	467.76	(17.04)	467.91	(1.00)	0.03%	(4.22%)
**Four Regions Combined*	18.96	(0.54)	19.90	(0.65)	4.96%	(4.13%)

Note: Of the four cortical ROIs, only the effect of the intervention on the left inferior frontal gyrus is statistically significant (Farah et al., 2021, Figure 3 and Table 7).

Table A2. Males: Means and (Standard Errors) of Brain Region Volumes for Control and Intervention Groups.

Group	Control (N=9)		Intervention (N=14)		Difference	
Volume in cc of:						
Brain	938.11	(14.84)	1030.91	(20.45)	9.89%	(2.18%)
Cortex	433.78	(7.80)	480.33	(9.29)	10.73%	(2.14%)
**AntCingGyrus*	4.79	(0.27)	6.24	(0.19)	30.37%	(4.04%)
**LeftSupTempGyrus*	4.71	(0.16)	5.11	(0.15)	7.84%	(3.22%)
**RightInfFrontGyrus*	4.32	(0.15)	5.36	(0.18)	23.88%	(4.29%)
**LeftInfFrontGyrus*	4.72	(0.13)	5.30	(0.16)	14.19%	(3.31%)
Remaining Cortex	415.21	(7.68)	458.24	(9.13)	10.36%	(2.87%)
Remaining Brain	504.33	(8.85)	550.58	(12.78)	9.17%	(3.08%)
**Four Regions Combined*	18.57	(0.47)	22.09	(0.46)	19.00%	(3.54%)

Note: Of the four cortical ROIs, the effects of the intervention on all except the left superior temporal gyrus are statistically significant (Farah et al., 2021, Figure 3 and Table 7).

Appendix B: ANOVA of effects of intervention on IQ

Table B1. ANOVA of Effects of Intervention on IQ.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	1763.5	15.70	0.00029	0.00060
Sex	1	10.4	0.09	0.7624	0.9608
Intervention x Sex	1	5.5	0.49	0.8268	0.9412
Residuals	41	112.3			

Note: It is worrisome when an F-statistic, whose expected value under the null hypothesis is 1.0, is much smaller than its expectation, as it is for the F-value associated with the Sex factor. In this case it is reassuring that the reciprocal, 112.3/10.4 = 10.8, an F-statistic with 31 and 1 df, is far from significant.

Appendix C: ANOVAs of the effects of intervention on raw and normalized brain volume

Table C1. ANOVA of the Effects of Intervention on Raw Brain Volume.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	27666	5.98	0.019	0.044
Sex	1	186127	40.25	0.0000	0.0000
Intervention x Sex	1	23153	5.01	0.030	0.087
Residuals	43	4624			

Table C2. ANOVA of the Effects of Intervention on Normalized Brain Volume.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	300	5.29	0.026	0.016
Sex	1	422	7.44	0.0092	0.057
Intervention x Sex	1	262	4.63	0.037	0.062

(Continued)

Table C2. Continued.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Residuals	43	57			

Note: Partly because of the systematic differences in brain volume $\{v_i\}$ between males and females, these data were normalized, using the corresponding sex-specific control means, $\{\overline{v_c}\}$, expressing the results as percentage differences relative to the corresponding control mean: $100(v_i - \overline{v_c})/\bar{v}_c$.

Appendix D: ANOVAs of the effects of intervention on raw and normalized cortex volume

Table D1. ANOVA of the Effects of Intervention on Raw Cortex Volume.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	7102	7.32	0.019	0.0097
Sex	1	43553	44.91	0.0000	0.0000
Intervention x Sex	1	5679	5.86	0.0198	0.036
Residuals	43	970			

Table D2. ANOVA of the Effects of Intervention on Normalized Cortex Volume.

Source	Df	MeanSquare	F-Value	P_F	P_{perm}
Intervention	1	362	6.51	0.014	0.010
Sex	1	483	8.69	0.0051	0.024
Intervention x Sex	1	300	5.40	0.025	0.047
Residuals	43	56			

Appendix E: Properties of the four cortex regions included in the cognitive ratio

Table E1. Volumes of Four Cortical Regions as Mean Percentages of Cortex Volume in Male and Female Control and Intervention Groups.

	Control			Intervention		
Region	Male %	Female %	Diff %	Male %	Female %	Diff %
Bilateral anterior cingular gyrus	1.11	1.36	+0.25	1.30	1.36	+0.06
Left superior temporal gyrus	1.09	1.14	+0.05	1.07	1.10	+0.03
Right inferior frontal gyrus	1.00	1.13	+0.13	1.12	1.22	+0.10
Left inferior frontal gyrus	1.09	1.12	+0.03	1.12	1.27	+0.15
Total	4.29	4.75	+0.46	4.61	4.95	+0.33

Table E2. Percentage Bend Correlations of Volumes of Four Cortical Regions with Volumes of Whole Brain, Cortex, and Remaining Brain in Male Intervention Subjects.

	Brain	Cortex	Remaining Brain
Bilateral anterior cingular gyrus	−0.34	−0.33	−0.28
Left superior temporal gyrus	−0.44	−0.38	−0.46
Right inferior frontal gyrus	−0.43	−0.42	−0.40
Left inferior frontal gyrus	−0.52	−0.51	−0.42

Table E3. Pearson Correlations of Volumes of Four Cortical Regions with Volumes of Whole Brain, Cortex, and Remaining Brain in Male Intervention Subjects.

	Brain	Cortex	Remaining Brain
Bilateral anterior cingular gyrus	−0.37	−0.28	−0.38
Left superior temporal gyrus	−0.43	−0.39	−0.39
Right inferior frontal gyrus	−0.43	−0.39	−0.40
Left inferior frontal gyrus	−0.42	−0.37	−0.40

Appendix F: Values of cognitive ratio and brain volume for four groups of subjects

Table F1. Values of cognitive ratio (in percent) and brain volume (in cc).

Intervention				Control			
Females		Males		Females		Males	
Ratio	Volume	Ratio	Volume	Ratio	Volume	Ratio	Volume
4.23	848.0	3.93	1136.1	4.20	949.6	3.76	893.4
4.49	849.9	4.09	1155.1	4.33	830.2	3.88	968.1
4.53	872.9	4.39	1035.9	4.55	885.2	4.10	967.9
4.65	906.8	4.39	1101.3	4.68	974.2	4.10	1018.3
4.71	949.6	4.40	985.0	4.70	828.9	4.43	946.7
4.72	824.8	4.48	1032.5	4.91	899.1	4.44	931.8
4.96	823.2	4.49	967.0	5.02	843.2	4.44	913.2
5.10	751.4	4.50	1119.1	5.12	691.6	4.64	935.4
5.21	870.7	4.54	1028.1	5.19	914.9	4.80	868.1
5.30	897.1	4.61	1084.3				
5.30	934.8	4.68	885.0				
5.32	820.9	5.02	936.6				
5.33	894.5	5.11	1063.5				
5.38	935.4	5.12	973.0				
		5.48	961.1				

Appendix G: Ancillary findings related to the cognitive ratio and to distinctive features of the male intervention group

First, consider the numerator of the cognitive ratio (summed volume of four cortical regions of interest, "Sum4" in the tables below), its denominator (cortex volume), and their ratio. For subjects in the male intervention group, the numerator is not correlated with volume of the remaining brain (whole brain less cortex), while the cognitive ratio, as we have seen, is correlated negatively. In contrast, for subjects other than those in the male intervention group, the numerator and denominator are each correlated positively with the volume of the remaining brain, but, as we have seen, the cognitive ratio itself is not.[15] These differences between the correlation pattern of the cognitive ratio and that of its numerator (a more traditional measure) suggests that they reflect different aspects of brain function.

Table G1. Correlations of Volumes of Three Regions with Volume of Remaining Brain: Male Intervention Participants.

Correlation Type	Percentage Bend		Pearson	
Region	Correlation	*P*-value	Correlation	*P*-value
Sum4	+0.01	0.97	+0.01	0.97
Cortex	+0.73	0.002	+0.71	0.004
Cognitive Ratio	−0.54	0.036	−0.57	0.08

Table G2. Correlations of Volumes of Three Regions with Volume of Remaining Brain: Remaining Participants, using Adjusted Volumes for Females.

Correlation Type	Percentage Bend		Pearson	
Region	Correlation	*P*-value	Correlation	*P*-value
Sum4	+0.37	0.037	+0.36	0.025
Cortex	+0.55	0.001	+0.65	0.001
Cognitive Ratio	−0.04	0.85	−0.06	0.73

Second, consider correlations of the four-year IQ with (adult) brain volumes. For the male intervention group, correlations of IQ with volumes of cortex, remaining brain, and sum4 are small and nonsignificant. In contrast, for subjects other than those in the male intervention group, IQ is positively correlated with both the numerator and denominator of the cognitive ratio, and with remaining brain volume. The correlation with cognitive ratio is small, negative, and nonsignificant for both groups.

Table G3. Correlations of IQ with Brain Volumes and Cognitive Ratio: Male Intervention Subjects.

Correlation Type	Percentage Bend		Pearson	
Region	Correlation	*P*-value	Correlation	*P*-value
Sum4	−0.14	0.61	−0.11	0.73

(*Continued*)

[15]As discussed in note 11, female volumes were multiplied by 1.11, to avoid spurious effects of the systematic difference between male and female brain volumes.

Table G3. Continued.

Correlation Type Region	Percentage Bend Correlation	Percentage Bend *P*-value	Pearson Correlation	Pearson *P*-value
Cortex	+0.14	0.61	+0.13	0.68
Remaining Brain	0.00	1.00	−0.03	0.91
Whole Brain	+0.02	0.95	+0.04	0.88
Cognitive Ratio	−0.32	0.24	−0.22	0.36

Table G4. Correlations of IQ with Brain Volumes and Cognitive Ratio: Remaining Subjects, using Adjusted Volumes for Females.

Correlation Type Region	Percentage Bend Correlation	Percentage Bend *P*-value	Pearson Correlation	Pearson *P*-value
Sum4	+0.30	0.11	+0.30	0.04
Cortex	+0.34	0.07	+0.37	0.04
Remaining Brain	+0.41	0.02	+0.45	0.01
Whole Brain	+0.41	0.02	+0.46	0.02
Cognitive Ratio	−0.07	0.71	−0.06	0.68

The differences between groups in the correlations of IQ with whole brain and remaining brain are especially noteworthy. How impressed should we be with these differences? One approach to determining whether the relation between IQ and a brain measure differs between the two groups is to fit a model in which IQ is treated as a linear function of the brain measure and group, and evaluate the interaction between the brain measure and group. When this is done for Whole Brain, $P_F = 0.09$ and $P_{perm} = 0.10$. When it is done for Remaining Brain, the corresponding values are $P_F = 0.07$ and $P_{perm} = 0.08$. We thus have weak evidence for the conclusion that whereas for females and control males, larger brain volume is associated with higher IQ, this association is absent for intervention males: for them, the gain in IQ due to the intervention is unrelated to the gain in brain volume. If this is true, it would make less puzzling the virtually identical gains in IQ for intervention males and females (Table 1) combined with their very different gains in brain volume (Table 2). Among this set of subjects, it is possible that a larger brain is associated with a higher IQ (Table G4), but not when its larger size is due to the intervention (Table G3).