Right Hippocampus-Amygdala Volume Robustly Predicts IQ

Paul J. Zak, PhD[*1], Rajaprabhakaran Rajarethinam, MD[2], Richard T. Gretz, MA[3], John R. DeQuardo, DO[4], and Rajiv Tandon, MD[5]

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Correspondence to: Paul J. Zak
Center for Neuroeconomics Studies
Claremont Graduate University, Claremont, CA 91711-6165
909-621-8788, FAX: 909-621-8460
paul.zak@cgu.edu

[*]1. **Corresponding Author**: Center for Neuroeconomics Studies, Claremont Graduate University, Claremont, CA 91711-6165, paul.zak@cgu.edu; and Department of Neurology, Loma Linda University, Loma Linda, CA 92350 2. Department of Psychiatry, Wayne State University, Detroit MI 48201; 3. Department of Economics, Claremont Graduate University, Claremont, CA 91711-6165 4.Colorado Mental Health Institute at Pueblo, Pueblo, CO 81003; 5. Department of Psychiatry, University of Michigan, Ann Arbor, MI.

Article abstract. *Background*: There is no consensus on the neural structures that produce intelligence. This is due to the statistical fragility of previous findings and the limited number of structures investigated. *Methods*: This study measures the volumes of 41 brain structures from T1-weighted MRIs of 20 normal male subjects who completed IQ tests. Our statistical method applies a robustness criterion and control covariates to determine neural structures that are uniformly significantly associated with IQ. Only two structures satisfy this restrictive statistical criterion: Right Hippocampus-Amygdala Complex (RHAC) and the right posterior hippocampus and amygdala (RHAP). These relationships hold both using absolute volume and relative to intracranial volume, controlling for age and education. Neither hippocampus nor amygdala volume alone is robustly statistically associated with IQ, nor are the volumes of other brain structures examined. The analysis establishes that a 1cc (19%) increase in RHAC is associated with a 7.6-point increase in IQ, while a 1cc (30%) increase in RHAP is associated with a 14.6 increase in IQ. *Conclusion*: There is a strong association between RHAC and RHAP volumes and two measures of intelligence.

1. Introduction

Human intelligence develops through the interaction of genetics and environment. While this is widely accepted [1-7], the neural structures associated with intelligence have not been clearly established. This is due, in part, to the statistical fragility of previous findings and the limited number of structures investigated. The present study uses volumetric magnetic resonance imaging (MRI) to measure 41 brain structures and relates these to intelligence as measured by Wechler Adult Intelligence Scale (WAIS) in 20 healthy individuals. We apply a restrictive statistical criterion to identify neural structures that are robustly statistically associated with IQ, and also include the control covariates age and education in all our analyses. In this way we seek to rule out statistical anomalies.

New brain imaging technologies offer the opportunity to characterize the neural basis for IQ. The majority of structural MRI studies have focused on IQ deficits associated with various disease syndromes, e.g. Cushing's disease [8], fragile X [9], temporal lobe epilepsy [10], schizophrenia [11], Parkinson's disease [12], reading disability [13], attention deficit disorder [14], head trauma [15], autism [16,17], sex chromosome aneuploides [18], headache [19]; as well as aging [20,21], while fewer have examined normal healthy adults.

The extant literature using normal subjects has found statistically significant correlations of Full-Score IQ and the volumes of the following structures: whole brain [22,23]; whole brain, cerebrum, temporal lobe, hippocampus, cerebellum [24]; frontal cortex [3,25]; cerebellum [26]; and gray matter [1]. Other studies find no results at all [27]. Not only is a consensus lacking on the brain structures associated with IQ, few studies examine volumetric correlations with Verbal IQ and Performance IQ (exceptions are [26] and [25]), or explore laterality differences. In sum, previous volumetric MRI research on IQ has found statistically fragile results in normals, has not comprehensively surveyed brain structures, and focused on statistical significance rather than statistical robustness.

The contributions of this study are i) to measure the volume of a much larger number of brain structures than has presently been done and relate these to IQ, and ii) apply a robustness test that rules out statistical aberrations. Regarding the first issue, Andreasen et al. [24] report measuring the volume of 13 regions, while Flashman et al. [25] measure 10 (counting left and right hemisphere structural volumes separately), while earlier studies measured fewer. Advances in imaging technologies now reliably permit volumes of

subcortical structures to be accurately determined. Including subcortical structures substantially broadens our analysis of the neural basis for IQ. Addressing the second issue, it is well-established that irrespective of sample size spurious statistical significance can appear among any set of variables [28]. The statistical fragility across studies in the literature indicates the need for a robustness criterion when associating regional brain volumes and IQ.

2. Materials and methods

Subjects: Twenty normal male subjects were recruited by advertisement. Because of well-established sexual dimorphisms in brain structures, only male subjects were included in this study. The mean age (SD) for subjects is 35 (15). After describing the study to subjects, written informed consent was obtained. None of the subjects had a history of neurological illness, head trauma, chronic medical illness or recent substance abuse, and subjects were screened using the normal control version of the Structured Clinical Interview [29] to exclude psychiatric disorders. Subjects with major mental illness in first-degree relatives were also excluded. The Wechsler Adult Intelligence Scale–Revised (WAIS-R) was administered to subjects to measure intelligence [30]. This test provides a measure of general intelligence (Spearman's "g") called Full-Score IQ (FSIQ), as well as the submeasures Verbal IQ (VIQ) and Performance IQ (PIQ).

MRI acquisition and processing: Sixty T1 weighted 3mm coronal slices, with no interslice gap, were obtained using a 1.5 T MR scanner (Signa, General Electric Medical Systems, Milwaukee) (3D SPGR coronal image series, matrix 256x256, 22 cm fovea, TR 40 msec., TE 5 msec., one excitation). The images were processed on a Silicon Graphics workstation using 'BRAINS' software [31] by research staff blind to subject information. First, the whole brain (cerebrum and cerebellum) was traced manually on the 3mm coronal slices. Using 'training classes', representative pixels of gray matter from the caudate and CSF from the lateral ventricle, a threshold pixel value was determined and used to delineate CSF from tissue on each image. The software then 'washed out' CSF pixels for each image, and calculated whole brain tissue (gray and white matter) volume by counting the number of tissue pixels multiplied by slice thickness. Following this procedure, the anterior commissure (AC) and posterior commissure (PC) points were manually located.

The whole image was then resampled (not morphed) into 3D Talairach space using the AC and PC points and whole brain outlines [32]. Resampling eliminates head position variation in three dimensions but does not change the size of the brain. The resampled image was used for manually tracing brain structures of interest.

Definition of regions of interest (ROI) and volumetric measurement: The ROIs, which constitute regions that we hypothesize may be associated with IQ, were chosen by surveying the relevant literature. Forty-one brain structure or substructure volumes were measured in the left and right hemispheres using BRAINS following the measurement methodology of Andreasen et al. [24] Intracranial volume, frontal lobe, parietal lobe, temporal lobe, occipital cortex, cerebellum, ventricles, brain stem, aggregate subcortical gray matter (caudate nucleus, putamen, and thalamus) were measured by an automated method using Talairach coordinates [31,33]. Manual tracings were used to determine volumes of the thalamus, caudate, hippocampus (total, anterior, posterior), amygdala, hippocampus amygdala complex (HAC) (total, anterior, posterior), and the superior temporal gyrus (total, anterior one-half, posterior one-half). The methods are described in earlier publications [11,34].

We describe the measurement of the HAC as an example. The posterior end of the HAC was defined as the coronal slice where the fornix first fully appears. The amygdala was traced anteriorly until it was no longer identifiable. Then, using the number of coronal slices this ROI was divided into three equal parts. When the HAC was not equally divisible by three, the middle and posterior thirds or the posterior third were assigned the additional slice(s). Visual inspection confirmed this division in each case, and avoids the potential bias and variability inherent in manual methods used to measure these small structures**.** All ROIs were traced twice independently by one of the authors (RR). The test-retest reliability assessed by intraclass correlation was 0.57 on the right side and 0.79 for the left.

Statistical Analysis: A multiple regression model was run for the volume of each ROI against FSIQ and VIQ, including age and education as statistical controls. This approach takes into account the critiques raised for measurement consistency and proper controls [20,35]. Performance IQ has very little correlation with any regional brain structures in this sample as it draws on a diverse set of skills [36] and is therefore not used

in the analysis. All ROIs were not included in the analysis simultaneously due to the high correlation among ROI volumes [13], and because the large number of structures we examine causes a degrees of freedom problem for statistical tests.

Three sets of criteria were applied to determine if a robust correlation with IQ exists, i) all correlations utilize age and education as covariate controls; ii) the partial correlation of an ROI's volume is statistically significantly related to both FSIQ and VIQ; and, iii) statistical significance for a region obtains using both absolute volume and volume relative to intracranial volume (ICV). If a brain region satisfies all these conditions, we are confident that the findings are not spurious. Besides the volume of whole structures, the volumes of subcortical structures that the literature reports as statistically significant were examined by parsing them into subregions, e.g. the anterior half and posterior half of the hippocampus.

3. Results

For subjects in the sample, mean (SD) ICV is 1479cc (113cc). Throughout, all volumes are reported in cubic centimeters (cc), and we subsequently suppress the units. Subjects' average (SD) FSIQ and VIQ are 113.7 (11.8) and 112.3 (12.1). The average subject in the sample has 16 (2.2) years of education. Below, we use "R" and "L" to identify lateralized structures, e.g. RHAC is right hippocampus amygdala complex.

Our primary finding is that right hippocampus amygdala complex (RHAC) volume satisfies the robustness criterion for statistical significance and is positively related to IQ. Considering histological and possible functional variations in HAC, we also examined its subdivisions. A combination of the posterior one-half of the right hippocampus and the right amygdala (denoted right hippocampus amygdala posterior one-half, or RHAP) also satisfies the criterion for robust statistical significance and is positively related to IQ. None of the 38 other brain structure or substructure volumes measured are robustly statistically related to IQ. Figure 1 plots RHAC volume, both absolute and relative to ICV, and FSIQ, and shows an ordinary least squares regression line through these data. The plots for RHAP are similar.

Table 1 reports the regressions that attain statistical significance and are robust. Several regions (left anterior one-third superior temporal gyrus (-), left parietal lobe/ICV (-))

showed occasional statistical significance with FSIQ or VIQ, but not robust significance as defined above. Because of the moderate sample size, we applied the Jarque-Bera test for normality to determine if standard statistical tests that are based on a t distribution in finite samples and asymptotic normality can be used. The last row in Table 1 shows that all regression errors are normally distributed so that a t-test of statistical significance is appropriate for these data. The table shows that age and education alone explain 51% of the variation in FSIQ and 40% of VIQ. The addition of RHAC increases the explained variation in FSIQ by 25% and VIQ by 35%, while RHAP increased baseline explained variation by 35% for FSIQ and 50% for VIQ. There is no statistically significant IQ difference for left- or right-handed individuals.

Other ROIs that attained statistical significance in any of the four regressions (absolute volume or volume/ICV on FSIQ or VIQ) were then re-examined using additional statistical tests. These tests re-estimated the VIQ and FSIQ regressions with the age and education controls, and included the ROI being investigated as well as either RHAC volume or RHAP volume in the same equation. In every case, the new ROI did not attain statistical significance, while RHAC or RHAP continue to maintain significance. This indicates that RHAC and RHAP are strongly associated with FSIQ and VIQ even in the presence of other covariates.

Our statistical analysis establishes that a 1cc (19%) increase in RHAC volume is associated with a 7.6 point increase in FSIQ, and 7.8 point increase VIQ; a 1cc (30%) increase in RHAP volume is associated with 14.6 point and 15.5 point increases in FSIQ and VIQ, respectively.

4. Discussion

The analysis reported here suggests a role for the right hippocampus and amygdala in general and verbal intelligence in males. In the hippocampal memory system, the hippocampus and amygdala are functionally complementary, with the former mediating spatiotemporal context while the later mediates affective cues [37-40]. Our results indicate that working memory, including visual-spatial components and the emotional content of memories, are important aspects of intelligence. Though the analysis is correlational, the presumed causal mechanism is increased neuronal and/or dendritic density leading to

enhanced functionality. The putative sources of highly developed visual and emotional memories are both genetic and environmental.

Based on our sample, IQ is not associated with whole brain volume, but with right hippocampus amygdala volume. While all brain regions presumably contribute to intelligence, RHAC and RHAP appear to be particularly important. Note that the HAC projects to the orbitofrontal and medial frontal cortices, areas that play a role in psychomotor executive function [41]. Our results may partially derive from the increase in amygdala volume relative to ICV of males (but not females) during childhood and adolescence [42]. Yet, the combined contribution of hippocampus and amygdala to intelligence appears to be central as neither structure alone is robustly related to IQ. Hippocampus, amygdala, or HAC volumetric changes are associated with a variety of disease states, including schizophrenia [11], post-traumatic stress syndrome, Cushing's disease, recurrent depression [43], severe childhood sexual abuse [44], anorexia nervosa [45], borderline personality disorder [46], and bipolar disorder [47]. The results here suggest that these diseases may impair cognitive abilities.

The correlations of RHAC and RHAP with IQ are particularly compelling given recent reports of neurogenesis in the adult human hippocampus [48,49]. Relatedly, treatment for Cushing's disease has been associated with hippocampal cell production [50]. In addition, a recent study reported adult neurogenesis in the amygdala of two species of nonhuman primates [51]. The implication of these studies and our work is that intelligence in adults may be more plastic during disease states than had previously been thought [36].

Limitations: Replications in larger samples are important to corroborate the role of the HAC in intelligence. The results here may not generalize to females who have not been included in this study. Indeed, a recent PET study shows recall of emotional images by men activated the right amygdala, while the same task in women activated the left amygdala [52]. The histological subdivisions and the distribution of the nuclei in hippocampus and amygdala are intricate and were not measured in the present study. The findings should therefore be viewed as preliminary. Further, RHAC and RHAP explain only a small proportion of the variation in IQ indicating that other factors not included in this study also contribute to intelligence [53].

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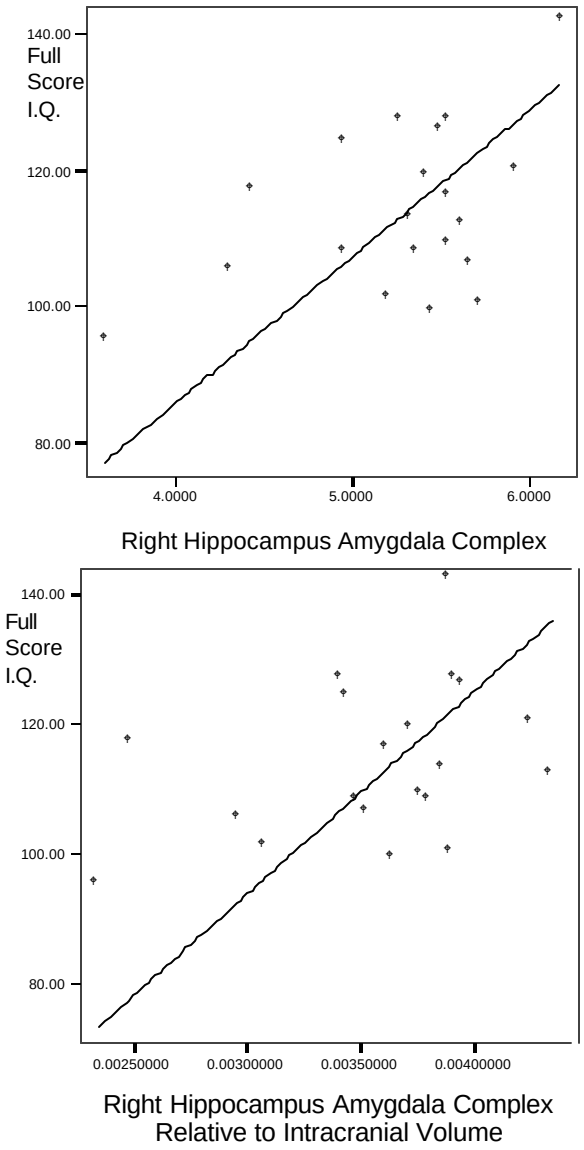

Fig. 1. RHAC and FSIQ for 20 male subjects with a linear regression line through the data showing a positive relationship.

	1		2		3		4		5	
	Full Score I.Q.	Verbal I.Q.	Full Score I.Q.	Verbal I.Q.	Full Score I.Q.	Verbal I.Q.	Full Score I.Q.	Verbal I.Q.	Full Score I.Q.	Verbal I.Q.
Constant	57.008	56.105	17.947	17.869	28.945	27.238	7.521	2.840	17.392	11.328
Education	2.817***	2.731***	2.939***	2.768***	2.856***	2.699***	2.992***	2.949***	2.884***	2.820***
Age	0.331**	0.385**	0.252*	0.280*	0.312**	0.344*	0.284**	0.344**	0.343***	0.402**
RHAC			7.583**	7.828***						
RHAC / ICV					7853.2**	8565.2**				
RHAP							14.643***	15.536**		
RHAP / ICV									16998.6***	19070.3***
R-Squared	0.505	0.397	0.641	0.540	0.624	0.537	0.688	0.603	0.681	0.619
Jarque-Bera Normality Test	1.008	0.219	0.546	1.424	1.310	0.790	1.222	1.742	1.799	1.188

Notes: *** is ≥ .01 significance; ** is ≥ .05 significance; * is ≥ .10 significance

Table 1. Multiple regression results for IQ measures regressed on RHAC and RHAP volumes, with and without controlling for ICV.