Hippocampal Size Positively Correlates With Verbal IQ in Male Children

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ABSTRACT: Historically, there have been numerous proposals that the size of the brain correlates with its capacity to process information. Little is known, however, about which specific brain regions contribute to this correlation in children and adolescents. This study evaluated the relationship between intelligence and the size of various brain structures in typically developing male children 8–18 yrs of age. Magnetic resonance imaging (MRI) scans were used to measure the volume of the cerebrum, cerebral gray and white matter, cerebellum, amygdala, and hippocampus. Gray matter and hippocampal volume significantly correlated with full scale and verbal IQ. Since the hippocampus strongly correlated with verbal but not performance IQ, our findings reinforce the hypothesis that the hippocampus is involved in declarative and semantic learning, which contributes more notably to verbal IQ, than to performance IQ. Given the substantial evidence for environmentally induced changes in hippocampal structure, an unresolved issue is whether this relationship reflects genetically determined individual variation or learning induced plasticity. © **2007 Wiley-Liss, Inc.**

KEY WORDS: intelligence; brain volume; hippocampus; amygdala; cerebral gray

INTRODUCTION

The brain in typically developing male children reaches ~90% of its adult size by age six and slowly continues to increase in size until around 15 years of age (Giedd, 1999; Giedd et al., 2004). Many factors contribute to brain tissue volume, including the number and size of neurons and glial cells, the number and collateralization of afferent and efferent fibers, myelination, and even the density of vasculature. An enriched environment increases the size of certain brain regions, in part, because of neurogenesis and increasing the complexity of connections (Diamond, 2001; Grossman et al., 2002). There have been numerous proposals that the size of brain regions correlates with information processing capacity. For example, the increased size of the cerebral cortex in human vs. other primates and rodents has been suggested to be the result of the development of many more cortical columns leading to enhanced cognitive ability and intelligence (Gibson, 2002; Krubitzer and Kahn, 2003).

The speculation that larger brain size may result in greater information processing capacity has led to an examination of the relationship between brain size and intelligence quotient (IQ) measures. Even prior to the advent of MRI, the relationship between intelligence and "brain size" was evaluated by using external measurements of the head (Van Valen, 1974; Lynn, 1993). Willerman et al. (1991) were the first to examine the correlation of actual brain size, determined by MRI, and intelligence. They found that larger brain size, after adjusting for body size, is associated with higher IQ in college students. Several MRI studies have since confirmed Willerman et al. (1991) and found an average correlation of brain size and intelligence of 0.40 (Andreasen et al., 1993; Raz et al., 1993; Egan et al., 1994; Wickett et al., 1994; Reiss et al., 1996).

There is some evidence that the correlation between brain size and IQ is driven primarily by differences in gray matter, which is more apparent in particular brain regions. For example, although full scale IQ positively correlates with whole brain gray matter volume in children (Reiss et al., 1996) and adults (Andreasen et al., 1993; Wilke et al., 2003), Reiss et al. (1996) found that the variance in IQ measures is mainly accounted for by the prefrontal cortex. Recently, Giedd and colleagues (Shaw et al., 2006) found the thickness of the cortex to be positively correlated with intelligence in late childhood, particularly in the prefrontal region.

Although twin studies reveal strong genetic influences on overall brain and gray matter volume (Andreasen et al., 1993; Wilke et al., 2003), the size of some structures, such as the hippocampus, are less heritable (Bartley et al., 1997; Sullivan et al., 2001; Thompson et al., 2001). It is well documented that the hippocampus can undergo environmentally induced increases in size (Maguire et al., 2000, 2003) with numerous reports of postnatal neurogenesis and synaptogenesis (Kempermann et al., 1997; Nilsson et al., 1999; Brown et al., 2003). One might hypothesize that the size of structures such as the hippocampus that are intimately involved in learning and memory, would be more likely to correlate with intelligence

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measures than, for example, structures, such as the amygdala, that are involved in the regulation of emotions. Andreasen et al. (1993) found that the size of the hippocampus correlated with IQ measures in typical adults, but this topic has yet to be explored in children. This study sought to evaluate the relationship between intelligence, as assessed with IQ measures, and the size of brain structures, including total cerebrum, cerebral gray matter, cerebral white matter, total cerebellum, cerebellar core white matter, cerebellar hemispheres, cerebellar vermis, hippocampus, and amygdala volumes, in preadolescent and adolescent typically developing male children.

METHODS

Diagnostics

A parent or guardian for each study participant gave informed consent, and the study participant gave their assent to participate in these studies as approved by the Institutional Review Boards of the University of California, Davis and Stanford University. Study participants were recruited as part of a larger study on autistic spectrum disorders through the UC Davis M.I.N.D. Institute and Stanford Neuropsychiatry Clinic. Twenty-seven right-handed typically developing male volunteers between the ages of 8.1–18.2 years (mean age 13.1 $\pm$ 3.1 years) participated in the study. To eliminate variability in brain measurements due to gender, only males were included in the study.

IQ assessments were conducted by trained researchers at either the UC Davis M.I.N.D. Institute clinic or at Stanford University in the division of Child and Adolescent Psychiatry and Child Development. Study participants were given the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), a nationally standardized abbreviated version of the Wechsler Intelligence Scale for Children (WISC-III) and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). The WASI yields three traditional IQ scores (verbal, performance, and full scale) with confidence intervals equivalent to the longer WISC-III measure. The Verbal Scale is composed of the Vocabulary and Similarities subscales that assess verbal knowledge, expressive vocabulary, and abstract verbal reasoning ability. The Performance Scale is composed of the Block Design subtest and the Matrix Reasoning subtest that tap spatial visualization, abstract conceptualization, and visual-motor coordination. Participants were considered typically developing if they had a full scale IQ above 70, did not have a neurological or psychiatric disorder including seizures, ADHD, obsessive-compulsive disorder, bipolar disorder, or autistic spectrum disorder, and did not have a family member with an autism spectrum disorder.

Neuroimaging

A parent or guardian for each participant signed consent prior to the child entering the MRI scanner and was present throughout the duration of the scan in an adjacent waiting room. Eighteen participants were scanned at the UC Davis Imaging Research Center (using a 1.5T GE Signa NV/I system) and nine participants were scanned at the Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging at Stanford University (using a 3T GE Signa VH/I system). The protocol for scanning each participant included a 3D coronal SPGR (spoiled gradient recalled echo) series (TR: 35 μs, TE: 6 μs, FOV: 24 cm, Matrix: 256 $\times$ 256, section thickness: 1.5 mm, number of slices: 124, total scan time: 14:24 min), which was used for the volumetric assessment of the cerebrum, cerebellum, hippocampus, and amygdala.

Since volume measurement accuracy is related to the linearity of magnetic field gradients in each of the MRI systems, an intersite comparison was performed using the same pulse sequence from three healthy adult volunteers (one male and two females) at each of the two MRI sites for in vivo validation of volume measurement accuracy. Images were analyzed at the Stanford Psychiatry Neuroimaging Laboratory using Brain-Image software (Reiss, 2002). The percent difference between MRI systems for each participant was averaged across participants to arrive at a mean percent difference for each volumetric measure. A 1.5% difference for total cerebral tissue and a 1.6% difference for cerebral gray matter were found. Differences in volume measurements of the cerebellum were greater than 5% between MRI systems. This is not surprising since structures closer to the end of the head coil are more susceptible to inhomogeneities in the magnetic field, particularly in higher strength magnet scanners. The cerebrum is typically placed in the less distorted center of the head coil and is therefore more consistently measured across scanners of varying strength. Hence, data was not combined across sites for cerebellar measures. Lotspeich et al. (2004) have presented a more detailed description of site comparisons. Only participants imaged at UC Davis were included in the analysis of the cerebellum for this study. Analysis of cerebral gray matter, cerebral white matter, total cerebral volume, amygdala, and hippocampus volumes included all subjects scanned at UC Davis and Stanford University.

Volumetric Analyses

Following completion of the MRI acquisition, all images were transferred to UC Davis for volumetric analyses. Each coronal SPGR series was imported into ANALYZE 5.0 (Robb et al., 1989) and manually outlined. After reviewing the images, five participants (four from UC Davis and one from Stanford) were excluded from the study because of excessive movement or distorted images resulting from orthodontics. Excluded participants did not differ from included participants with respect to age or IQ.

Each series of images was manually segmented to remove nonbrain tissue, brainstem, colliculi, cerebellum, and lateral ventricles. Prior to classification of the cerebrum into gray and white matter, the images were normalized over 0–255 intensity range. This resulted in a predictable bimodal intensity histogram. Tissue classes were defined as plus or minus two standard deviations from the mode of each curve. All values lower than two standard deviations from the mode of the gray matter

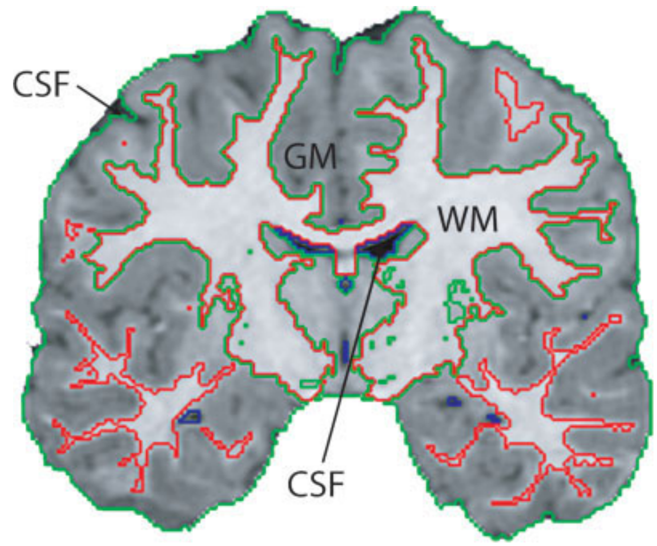

FIGURE 1. Coronal section through the brain displaying segmentation of cerebrum into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) for volume measurements.

curve were assigned to a CSF/Background class. The image was classified into objects (gray, white, and CSF) using a neural network classifier to obtain volume measures of gray and white matter (Fig. 1). Two raters established an interrater reliability with an intraclass correlation of 95%. The sum of the gray and white matter volumes was used as a measure of total cerebral volume.

A detailed protocol for defining the cerebellum on MRI scans (Fig. 2) developed in our laboratory is available upon request. Briefly, coronal SPGR images collected from study participants at UC Davis were converted to 0.9375-mm cubic voxels and aligned along the axis of the anterior and posterior commissures. Cerebellar structures were first manually defined at 2-mm increments in the sagittal plane and then edited in the coronal and horizontal planes. The whole cerebellum was defined by excluding the superior cerebellar peduncle and tracing along the surface of the right and left hemispheres. Cerebellar hemispheres were then delineated from vermis and subdivided into folia and medullary core white matter. Two raters established an interrater reliability with an intraclass correlation of greater than 90% for all cerebellar structures. Volumetric measures were taken of the total cerebellum, total right and left hemisphere folia, total right and left hemisphere core white matter, and vermis.

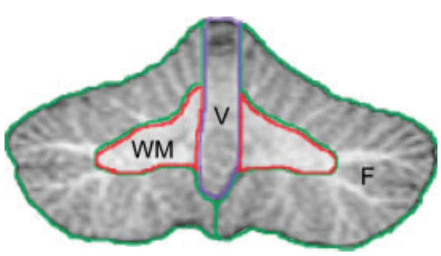

FIGURE 2. Coronal section displaying segmentation of the cerebellum into hemisphere core white matter (WM), hemisphere folia (F), and vermis (V) for volume measurements.

A detailed protocol for defining the hippocampus and amygdala on MRI scans (Fig. 3) has been provided elsewhere (Schumann et al., 2004). Briefly, coronal SPGR images collected from study participants at UC Davis and Stanford University were converted into 0.469-mm cubic voxels and reoriented along a horizontal axis from the rostral to the caudal pole of the hippocampus. The hippocampus and amygdala were first manually outlined on coronal sections and then edited in the sagittal and horizontal planes. Two raters established an interrater reliability with an intraclass correlation of 92% for the amygdala and 96% for the hippocampus. Volumetric measures were taken from the right and left hippocampus and amygdala.

Statistical Analyses

A two-tailed Pearson correlation was carried out to detect potential relationships of mean structural volumes, age of participant at time of MRI, and full scale, verbal, and performance IQ measures using Statistical Program for the Social Sciences Edition 12.0 software (SPSS, Chicago, IL, 2002). Some studies suggest that a larger surface area of the body may result in greater somatotopic representation in the brain (Peters, 1993). Therefore, a partial correlation of structural volumes and IQ scores, controlling for the height of the study participant, was calculated to account for body size. Age was also included as a variable in the partial correlation calculation for all structures. Gray matter volume was included as a variable in the partial correlation calculation for the amygdala and hippocampus.

RESULTS

Full scale IQ for study participants ranged from 93 to 133 with a mean of 115 ± 11. The age of the study participant at time of MRI did not correlate with any of the IQ measures

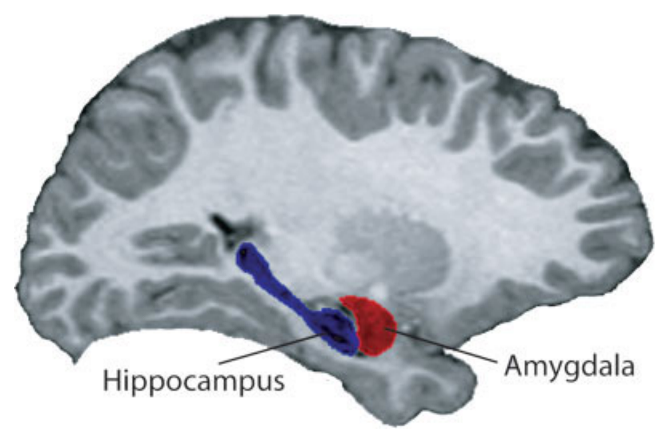

FIGURE 3. Sagittal section through the brain displaying manual outline of the amygdala and hippocampus for volume measurements.

TABLE 1.

Diagnostic Data for All Typically Developing Male Participants (n = 22)

	Mean	SD	Min.	Max.
Age at MRI (yr)	13.1	±3.1	8.1	18.2
Full scale IQ	115	±11	93	133
Verbal IQ	112	±14	85	134
Performance IQ	114	±12	91	136

(Table 1). There was a trend for total cerebral volume (Table 2) to correlate with full scale ($r = 0.41$, $P = 0.06$) and verbal IQ ($r = 0.38$, $P = 0.08$), but not performance IQ (Table 3). Cerebral gray matter volume (Fig. 4) significantly correlated with full scale ($r = 0.46$, $P < 0.05$) and verbal IQ ($r = 0.43$, $P < 0.05$), but not performance IQ. Although gray matter volume did not significantly correlate with the age of the participant, age was included as a variable in the partial correlation calculation. After correcting for the age and the height of the study participant, gray matter was not significantly correlated with IQ measures (full scale IQ $r = 0.38$, verbal IQ $r = 0.36$). Cerebral white matter, total cerebellar, cerebellar core white matter, cerebellar folia, and vermal volumes did not correlate with any of the IQ measures (Table 3).

The strongest relationships that we observed between brain size and IQ came from measurements of the hippocampus. Right hippocampal volume significantly correlated with full scale ($r = 0.58$, $P < 0.01$) and verbal IQ ($r = 0.60$, $P < 0.01$), but not performance IQ (Table 3). Left hippocampal volume also significantly correlated with full scale ($r = 0.59$, $P < 0.01$) and verbal IQ ($r = 0.73$, $P < 0.01$), but not performance IQ. Total hippocampal volume (left and right sides) (Fig. 5) correlated with full scale ($r = 0.60$, $P < 0.01$) and verbal IQ ($r = 0.69$, $P < 0.01$). Although hippocampal volume did not significantly correlate with the age of the participant, age was included in the partial correlation calculation. Hippocampal volume remained significantly correlated with full scale and verbal IQ measures at $r = 0.54$ ($P < 0.05$) and $r = 0.69$ ($P < 0.01$), respectively, after controlling for participant height, age, and overall gray matter volume. Amygdala volumes did not correlate with any of the IQ measures (Table 3).

DISCUSSION

This study is consistent with the previous observations in finding an average correlation of cerebral volume and intelligence of ~0.40 (Willerman et al., 1991; Andreasen et al., 1993; Raz et al., 1993; Egan et al., 1994; Wickett et al., 1994; Reiss et al., 1996). With advances in MRI analysis techniques, recent studies have further segmented the brain into gray and white matter. Our study replicated findings of a significant positive correlation of gray matter volume and full scale IQ (Andreasen et al., 1993; Reiss et al., 1996). Reiss et al. (1996) studied 85 typically developing children ranging from 5 to 17 years of age and found that cerebral gray matter predicted ~15% of the variance in IQ. This study confirms that the volume of cerebral gray matter is associated with higher intelligence in typically developing males 8–18 years of age, and predicts ~20% of the variance in IQ measures.

This study also sought to determine whether specific structures contributed to the positive correlation of gray matter and intelligence. We found a strong positive correlation of hippocampal volume with measures of full scale and verbal IQ even after correcting for the height, age, and gray matter volume of the participant. Andreasen et al. (1993) studied 67 adults and is the only other study to report a positive correlation of hippocampal size with IQ measures. This study extended that finding to children and adolescents. The volume of the hippocampus ranged from ~4.5 to 6.5 cm^3 and predicted 36% of the variance in full scale IQ and 47% of the variance in verbal IQ in typically developing males 8–18 years of age. Study participants with a verbal IQ above 120 had a 25% larger hippocampus than those with a verbal IQ below 100.

TABLE 2.

Volumetric Data in Cubic Centimeters (cm^3) for All Typically Developing Male Participants

Structural volume	Mean (cm^3)	SD (cm^3)	Min. (cm^3)	Max. (cm^3)
Total cerebral ($n = 22$)	1190	±77	1058	1338
Cerebral gray matter ($n = 22$)	808	±59	690	937
Cerebral white matter ($n = 22$)	388	±40	337	486
Total cerebellar ($n = 14$)	153	±12	133	171
Cerebellar core white ($n = 14$)	12.8	±2.1	9.2	17.4
Cerebellar hemisphere folia ($n = 14$)	123	±10	107	138
Cerebellar vermis ($n = 14$)	16.7	±1.9	14.3	20.0
Right amygdala ($n = 22$)	1.96	±0.25	1.57	2.53
Left amygdala ($n = 22$)	1.94	±0.28	1.52	2.41
Right hippocampal ($n = 22$)	2.75	±0.30	2.29	3.29
Left hippocampal ($n = 22$)	2.71	±0.32	2.20	3.33

TABLE 3.

Two-Tailed Correlation Data of Brain Structures and IQ Measures for Typically Developing Male Participants

Structural volume	Full scale IQ	Verbal IQ	Performance IQ
Total cerebral			
Pearson (*r*)	0.41	0.38	0.25
Sig. (*P* value)	0.060	0.079	0.265
Cerebral gray matter			
Pearson (*r*)	0.46	0.43	0.28
Sig. (*P* value)	0.032	0.045	0.205
Cerebral white matter			
Pearson (*r*)	0.36	0.34	0.17
Sig. (*P* value)	0.099	0.117	0.452
Total cerebellar			
Pearson (*r*)	0.12	–0.02	0.24
Sig. (*P* value)	0.689	0.942	0.416
Cerebellar core white			
Pearson (*r*)	0.17	–0.07	0.35
Sig. (*P* value)	0.566	0.821	0.221
Cerebellar hemisphere folia			
Pearson (*r*)	0.04	–0.09	0.19
Sig. (*P* value)	0.899	0.757	0.508
Cerebellar vermis			
Pearson (*r*)	0.36	0.42	0.09
Sig. (*P* value)	0.204	0.137	0.763
Right amygdala			
Pearson (*r*)	–0.03	0.03	–0.15
Sig. (*P* value)	0.906	0.934	0.503
Left amygdala			
Pearson (*r*)	–0.25	–0.20	–0.27
Sig. (*P* value)	0.262	0.367	0.233
Right hippocampal			
Pearson (*r*)	0.58	0.61	0.25
Sig. (*P* value)	0.005	0.003	0.260
Left hippocampal			
Pearson (*r*)	0.59	0.73	0.08
Sig. (*P* value)	0.004	0.000	0.728

These data are of interest in relation to the nature vs. nurture question of intelligence. Do some children have a higher IQ because they have a bigger hippocampus from birth and are therefore better able to learn and remember information, or does the size of the hippocampus reflect the quality and quantity of a child's educational experience? Data in support of either of these perspectives can be found in the literature. There is substantial evidence, for example, that the hippocampus can undergo environmentally induced increases in neuron number when rodents are placed in an enriched environment (Kempermann et al., 1997; Nilsson et al., 1999; Brown et al., 2003). Experience-induced neurogenesis in the hippocampus positively correlates with improvements on learning and memory tasks. Kempermann and Gage (2002) found a significant correlation between the level of new neurons in the dentate gyrus (DG) of the hippocampus and the level of performance on hippocampal-dependent tasks that involve the acquisition of new information. Species that develop complex spatial maps, such as food-caching birds, have larger hippocampi than members of the same species who do not engage in food caching (Clayton and Krebs, 1994), even though they have comparable sized hippocampi at birth (Clayton, 1998). Studies of experienced London taxi cab drivers who have memorized the complex roadway system of the city also have larger hippocampal volume than age-matched controls or newly licensed drivers (Maguire et al., 2000, 2003). It is not clear whether the process of learning the roadways induces an enlargement of the hippocampus or that only those individuals with a larger hippocampus, who are capable of memorizing the complexities of the roadways, ever succeed at the job.

Several factors may contribute simultaneously to both brain size and intelligence, including genetic influences, nutrition, and environmental stimulation (Ivanovic et al., 2004). However, the relationship of size and IQ is not common to all structures in the temporal lobe, since we found no relation between the volume of the amygdala and intelligence. This finding may presumably be accounted for by the nature of the IQ exam, which measures multiple domains of information processing that are performed by the hippocampus, such as memory formation (Squire and Zola, 1996; Zola et al., 2000; Manns et al., 2003a). A larger hippocampus could reasonably be associated with a greater ability to store and retrieve information that would be valuable in completing the exam. Functions performed by the amygdala, such as danger detection and the production of a fear response, are less likely to contribute to a higher score on an IQ exam.

One interesting aspect of our findings is that hippocampal volume strongly correlated with verbal, but not performance, IQ scores. The performance, or nonverbal, IQ score was determined by having an individual perform two activities involving spatial reasoning, pattern recognition, and visuomotor/coordination skills (Wechsler, 1999). The verbal IQ score was produced from two verbal tasks involving verbal knowledge, expressive vocabulary, and abstract verbal reasoning ability. The hippocampus is responsible for the encoding of declarative memory: both episodic information, i.e., memories of personal past experiences, and semantic information, i.e., general facts. Patients with bilateral hippocampal lesions, such as the well-known patient H.M., have intact visuomotor and perceptual abilities as well as procedural (or nondeclarative) learning (Milner, 1962; Corkin, 1968; Gabrieli et al., 1986; Shadmehr et al., 1998). However, H.M. and other hippocampal-damaged patients are severely impaired in declarative memory (Scoville and Milner, 1957; Milner, 1962; Gabrieli et al., 1988; Manns et al., 2003a). Thus, the hippocampus is responsible for learning factual information that is tested as part of the verbal IQ score. The hippocampus is not required, however, for skill learning, which contributes to the performance IQ score.

There are two opposing views in the literature regarding the role of the hippocampus in semantic memory. One view is that the hippocampus plays a unique role in episodic memory and that adjacent medial temporal structures support semantic memory (Tulving and Markowitsch, 1998; Vargha-Khadem

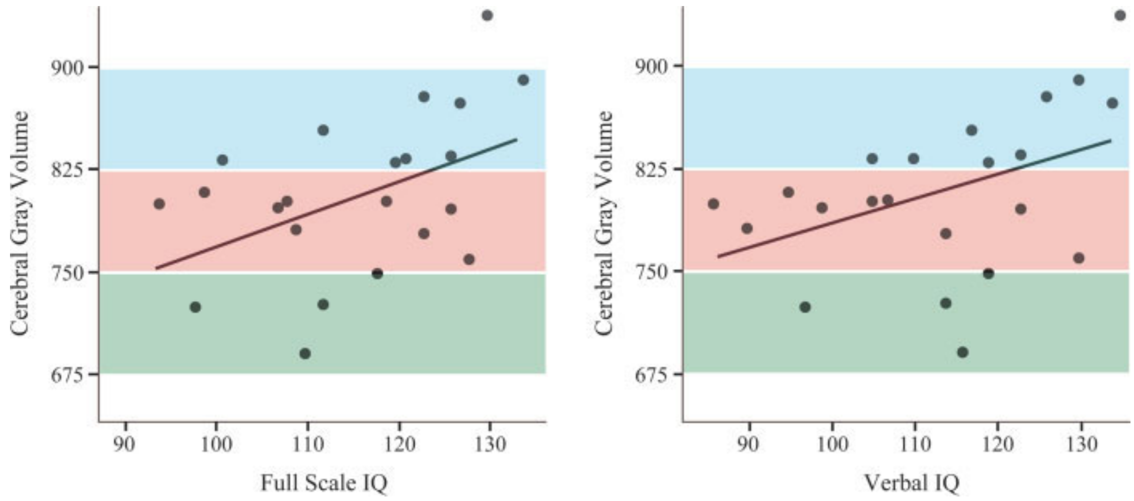

FIGURE 4. Linear regression scatterplot showing that cerebral gray matter volume measured in cubic centimeters (cm^3) in typically developing male children positively correlates with (a) full scale ($r^2 = 0.21$) and (b) verbal IQ ($r^2 = 0.19$).

et al., 1997). Another view is that the hippocampus is important for both episodic and semantic memory (Manns et al., 2003b). Vargha-Khadem et al. (1997) found that patients who sustained limited hippocampal damage early in life nevertheless attained levels of literacy and factual knowledge within the low to average range. The best studied case (Jon) performs normally on language and intelligence tests despite having an impaired episodic memory. However, Jon was impaired in learning facts (semantic memory) presented to him in the laboratory (Baddeley et al., 2001). It is also possible that early hippocampal damage provides an opportunity for functional reorganization or compensation through learned strategies, in which considerable semantic knowledge can be acquired throughout life without a fully functioning hippocampus. Our laboratory has provided evidence that while lesions of the hippocampus in mature rhesus monkeys leads to severely impaired use of spatial memory strategies, the same damage in neonatal monkeys does not impair spatial information processing when the animals are matured (Lavenex et al., 2007). This suggests that the early lesions have induced, in our monkeys and presumably in the children studied by Vargha-Khadem (1997), substantial morphological and functional reorganization.

Recently, Gogtay et al. (2006) investigated the trajectory of typical hippocampal development in a longitudinal MRI analysis of subjects between the ages 4 and 25. They found that the hippocampus undergoes a heterogeneous pattern of development, where the posterior end increases and the anterior end decreases in volume over this age range. Although Gogtay et al. (2006) suggests that the heterogeneous trajectory of the hippocampal subregions may parallel differences in functional development; they did not have longitudinal cognitive data to evaluate this hypothesis directly. Moreover, given the known highly associational

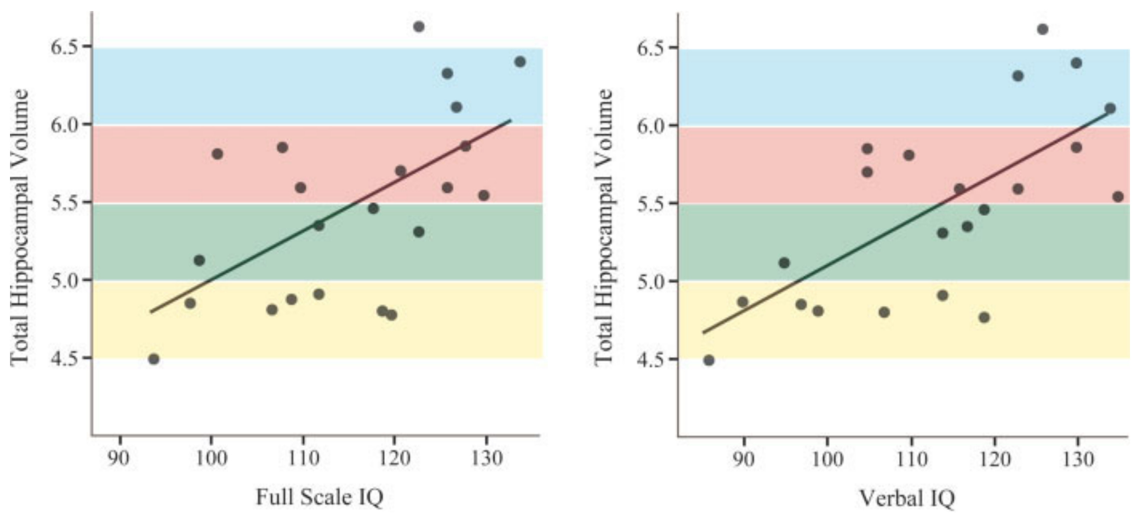

FIGURE 5. Linear regression scatterplot showing that hippocampal volume measured in cubic centimeters (cm^3) in typically developing male children positively correlates with (a) full scale ($r^2 = 0.36$) and (b) verbal IQ ($r^2 = 0.47$).

nature of hippocampal neuroanatomy (Lavenex and Amaral, 2000), subdividing the hippocampus into anterior and posterior sections is considered arbitrary. With the benefit of higher resolution MRI systems, it may be possible in the near future to parcellate the human hippocampus into cytoarchitectural subregions in order to correlate cognitive and behavioral capacities.

Given that the volume of the hippocampus accounts for a substantial proportion of the variability in verbal IQ, it would be of interest to determine if differences in hippocampal volume precede formal education or are a result of it. This could only be accomplished through a longitudinal MRI analysis that begins as early as possible after birth. Data of this type are currently being collected (Evans, 2006) and will afford an opportunity to test the hypothesis that hippocampal differences are observed prior to formal education. If hippocampal volume differences are observed prior to schooling, children with extremely small hippocampi may merit from educational practices that are less dependent on declarative memory and capitalize on procedural learning. To the extent that individual IQ scores may predict future success, so might early individual estimates of hippocampal volume.

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