Published in final edited form as:
Neuroimage. 2011 February 14; 54(4): 3093–3100. doi:10.1016/j.neuroimage.2010.11.021.

Beyond age and gender: Relationships between cortical and subcortical brain volume and cognitive-motor abilities in school-age children

Melissa M. Pangelinan[1], **Guangyu Zhang**[2], **John W. VanMeter**[3], **Jane E. Clark**[1], **Bradley D. Hatfield**[1], and **Amy J. Haufler**[1]

[1]Cognitive Motor Neuroscience Laboratory, Department of Kinesiology & Neuroscience and Cognitive Science Program, University of Maryland [2]Department of Epidemiology and Biostatistics, University of Maryland [3]Center for Functional and Molecular Imaging, Georgetown University Medical Center, Washington, DC, USA

Abstract

There is growing evidence that cognitive and motor functions are interrelated and may rely on the development of the same cortical and subcortical neural structures. However, no study to date has examined the relationships between brain volume, cognitive ability, and motor ability in typically developing children. The NIH MRI Study of Normal Brain Development consists of a large, longitudinal database of structural MRI and performance measures from a battery of neuropsychological assessments from typically developing children. This dataset provides a unique opportunity to examine relationships between the brain and cognitive-motor abilities. A secondary analysis was conducted on data from 172 children between the ages of 6 to 13 years with up to 2 measurement occasions (initial testing and 2-year follow-up). Linear mixed effects modeling was employed to account for age and gender effects on the development of specific cortical and subcortical volumes as well as behavioral performance measures of interest. Above and beyond the effects of age and gender, significant relationships were found between general cognitive ability (IQ) and the volume of subcortical brain structures (cerebellum and caudate) as well as spatial working memory and the putamen. In addition, IQ was found to be related to global and frontal gray matter volume as well as parietal gray and white matter. At the behavioral level, general cognitive ability was also found to be related to visuomotor ability (pegboard) and executive function (spatial working memory). These results support the notion that cognition and motor skills may be fundamentally interrelated at both the levels of behavior and brain structure.

Keywords

Structural MRI; IQ; Executive Function; Purdue Pegboard

Please send correspondence to: Melissa Pangelinan.
Present Address: Cognitive Motor Neuroscience Laboratory, Department of Kinesiology, 2351 School of Public Health Building, College Park, MD 20742-2611, USA, Phone: 301-405-2574, Fax: 301-405-5578, pangel@umd.edu

1. Introduction

Historically, the development of cognitive and motor skills in typically developing children has been studied and discussed separately, with only a few notable exceptions (McGraw, 1943; Piaget & Inhelder, 1969). However, there is growing evidence that these two domains are fundamentally interrelated across development (Diamond, 2000; Rosenbaum, Carlson, & Gilmore, 2001). Indeed, recent research suggests that these skills are not only interrelated at the behavioral level but may also rely on the development of similar cortical and subcortical neural structures (Davis et al., 2010; Diamond, 2000). Support for this notion comes primarily from children with developmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), dyslexia, and developmental coordination disorder (DCD) (Davis et al., 2009, Gilger & Kaplan, 2001; Piek & Dyck, 2004). Although these studies provide a basis for a relationship between cognitive and motor skills at the level of brain and behavior, evidence from developmental disorders may not hold true for typically developing children. Thus, the purpose of the current study is to address this knowledge gap by examining the trajectory of cortical and subcortical brain development with respect to both cognitive and motor skills in typically developing children.

Evidence from clinical populations has served as the basis for recent studies investigating the interrelation of cognitive and motor skills. In particular, children with developmental disorders such as ADHD and ASD, which are characterized predominantly as cognitive (attention) and socio-emotional (affective) disorders, respectively, also exhibit impaired motor functions. This includes: poor handwriting and fine motor skills (Fuentes, Mostofsky, & Bastian, 2009; Racine, Majnemer, Shevell, & Snider, 2008), difficulties planning movements (Eliasson, Rosblad, & Forssberg, 2004; Hughes, 1996; Rinehart, Bradshaw, Brereton, & Tonge, 2001), and poor gross motor coordination (Leary & Hill, 1996; Miyahara et al., 1997; Pitcher, Piek, & Hay, 2003). Consistent with these behavioral deficits, children with ADHD and ASD have been found to have structural abnormalities in brain regions that mediate both cognitive and motor circuits, including: subdivisions within the frontal cortex (Carper & Courchesne, 2000; Mostofsky et al., 2002), parietal cortex (Castellanos et al., 2002; McAlonan et al., 2005), striatum (Castellanos et al., 2002; Langen et al., 2009; Qiu et al., 2009), and cerebellum (Carper et al., 2000; Castellanos et al., 2002; Mostofsky, Reiss, Lockhart, & Denckla, 1998).

Similarly, children that have been identified as having movement coordination difficulties (i.e., DCD) also exhibit difficulties in executive cognitive function tasks that require inhibition, task switching, and working memory (Piek et al., 2004; Querne et al., 2008). Not surprisingly, the same brain regions implicated in ADHD and ASD have also been proposed to underlie behavioral deficits in DCD (Kaplan, Wilson, Dewey, & Crawford, 1998; Zwicker, Missiuna, & Boyd, 2009). Although the interrelation between cognitive and motor skills at both the behavioral and neuroanatomical levels has been well characterized in clinical pediatric populations, these relationships are much less clear typically developing children.

At the behavioral level, the relationship between motor development and cognitive development in typically developing children has only recently been investigated. For example, positive relationships have been reported between IQ and the movement speed during a sequencing task (Martin et al., 2010), motor proficiency and fluid crystallized intelligence (Davis et al., 2010), and motor performance and working memory (Wassenberg et al., 2005). Given the relationship between cognitive and motor skills at the behavioral level, these studies have suggested that similar neural etiology (e.g., development of frontal, parietal, cerebellar, and basal ganglia structures) may underlie the development of cognitive and motor skills.

Recent developmental neuroimaging studies have begun to map cortical brain structures with respect to cognition in typically developing children. These studies reported that IQ was correlated with measures of cortical thickness (Shaw et al., 2006), overall gray matter volume (Wilke, Sohn, Byars, & Holland, 2003), and regionally specific (prefrontal) gray matter volume (Reiss et al., 1996). Although Reiss et al. (1996) found that subcortical gray matter was also related to IQ, very little is known regarding the relationship between cognition and the development of specific subcortical brain areas including the basal ganglia structures (caudate, putamen, globus pallidus) and cerebellum. Given that several *functional* imaging studies of typically developing children and adults have implicated the caudate, putamen, and cerebellum in cognitive task performance (Luna et al., 2001; Rubia et al., 2006; Rubia, Smith, Taylor, & Brammer, 2007), it is likely that developmental changes in cognitive function would be related to the anatomical development of these structures. Although no studies to date have directly mapped visuomotor skills with respect to brain volume in typically developing children, it is likely that the development of motor skills, particularly those requiring bimanual visuomotor ability and fine motor control, may be related to the development of various brain regions extending beyond the motor cortex. Indeed, recent evidence from *functional* imaging studies in healthy adults suggests that improvements in visuomotor skill rely on the refinement of several functional networks among cortical (frontal and parietal) and subcortical brain regions that overlap considerably with the networks underlying cognitive or executive skills (Floyer-Lea & Matthews, 2004; Staines, Padilla, & Knight, 2002).

The NIH MRI Study of Normal Brain Development (Brain Development Cooperative Group & Evans, 2006) provides a unique opportunity to examine global and regional changes in brain volume with respect to performance on cognitive and motor tests from a large longitudinal sample of typically developing children. The current study aims to address the following knowledge gaps in the developmental cognitive neuroscience literature. First, are executive function (spatial working memory) and general cognition (intelligence) related to the development of cortical and subcortical brain regions that mediate both cognitive *and* motor skills? Second, what is the relationship between the structural brain development of cortical and subcortical regions and visuomotor skill? Third, what is the relationship between motor and cognitive development at the behavioral level?

To address these knowledge gaps, a subset of the original dataset which consisted of 172 prepubescent typically developing children between the ages of 6 and 13 years was analyzed using linear mixed regression models to characterize global (total gray and white matter) and regional volumes (frontal gray and white, parietal gray and white, cerebellum, caudate, putamen, and globus pallidus), intelligence, executive function (spatial working memory), and visuomotor skill with respect to age and gender effects. Subsequent analyses allow for the investigation of relationships above and beyond the well established effects of age and gender on cortical and subcortical brain volumes (De Bellis et al., 2001; Lenroot et al., 2007; Reiss et al., 1996; Sowell et al., 2002) as well as behavior (Waber et al., 2007). This approach enables *unique* relationships between brain and behavior to emerge, which might otherwise be obscured by age and gender effects. We hypothesized that generalized intelligence and executive function (spatial working memory) would be positively related to the volume of the cerebellum and basal ganglia, in addition to fronto-parietal cortical development. We also hypothesized that visuomotor skill development would be positively related to fronto-parietal cortical brain development. Moreover, at the level of behavior, cognitive ability (intelligence and executive function) would be positively related to visuomotor ability.

2. Material and Methods

The purpose of the NIH MRI Study of Normal Brain Development (funded by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke) was to provide a large, longitudinal public database (Pediatric MRI Data Repository) of demographic, behavioral, and anatomical brain data from healthy infants, children, and adolescents (Brain Development Cooperative Group & Evans, 2006). The list of participating sites and a complete listing of the study investigators may be found at http://www.bic.mni.mcgill.ca/nihpd/info/participating_centers.html. All procedures for the secondary analyses were approved by the Institutional Review Board (IRB) at the University of Maryland and in accordance with the NIH MRI Study of Normal Brain Development data access procedures. The testing procedures including the exclusion criteria, sample demographics, data acquisition parameters, MRI data processing, and performance of the full sample on the behavioral tasks have been reported previously (Brain Development Cooperative Group & Evans, 2006; Waber et al., 2007). For the current study, participant demographics, telephone screening, physical and neurological exam, pubertal status, segmented MRI volumes, as well as the behavioral performance on cognitive and motor tasks were obtained from the Pediatric MRI Data Repository (data release 2).

2.1 Subject Selection

A total of 490 observations from 315 children were obtained from the data repository for children between the ages of 6.00 and 12.99 years. Participants visited the laboratory on two occasions: an initial session and follow-up session approximately 2 years later (follow-ups ranged from 1.5 – 2.5 years). On each measurement occasion the children completed physiological screening including: a physical and neurological assessment, the pubertal development scale (Petersen et al., 1988), and provided saliva and urine samples. The children then underwent anatomical MRI scanning and completed a battery of behavioral tests. From the original data set, 172 children were included in the present secondary analysis based on the following additional exclusionary criteria: 1) failing the quality control standards for the MRI data acquisition (for full details see Brain Development Cooperative Group & Evans, 2006); 2) left-handed; 3) full scale IQ < 80; 4) history of head injuries or neurological deficits; 5) learning disability, including attention deficit hyperactivity disorder (ADHD) or enrollment in special education; and, 6) puberty development scale average score[1] > 2 (“barely started puberty”). Data from each measurement occasion were subjected to these criteria and may result in the loss of data from one or both measurement occasions for an individual participant.

Table 1 presents the sample characteristics for the current analysis. Of the 172 children, 45 (19 males and 26 females) provided complete measurements at both measurement occasions (1.5 – 2 years between measurements). The rest of the children either provided complete initial measurement but did not have a complete data set for the follow-up (70 children – 21 males and 49 females) or vice versa (57 children – 28 males and 29 females). The resulting statistical analysis for each dependent measure included 217 observations. Within subject associations, when applicable, were determined using the participant identification number and were accounted for by specifying the correlation structure for repeated measures.

[1]The pubertal development scale (PDS) consists of an interview that assesses physical development in the following areas for males: growth spurt, body hair, skin changes, facial hair, and voice changes. For females the scale assesses the following: growth spurt, body hair, skin changes, breast change, and menarche. Responses were coded on a 4-point scale: 1 = not started; 2 = barely started; 3 = definitely underway; and 4 = complete. The responses from the 5 items are averaged to maintain the original 1 – 4 scaling.

2.2 Behavioral Measures

The NIH MRI Study of Normal Brain Development consisted of performance measures from a battery of neuropsychological assessments (intelligence, verbal learning/fluency, executive function, fine motor dexterity, and academic skills). For the purpose of the current study, the following assessments were selected among the larger set of available neuropsychological measures. General intelligence was assessed with the Wechsler Abbreviated Scales of Intelligence (WASI – Wechsler, 1999) Full Scale IQ and comprised of performance on the following subtests: vocabulary, block design, similarities, and matrix reasoning. Spatial working memory was selected to represent one aspect of executive function and was assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB – CeNeS, 1998) spatial working memory task (SWM – total number of errors). For this computerized task, children were asked to sequentially point to boxes presented on the screen to determine which box contains a blue square without pointing to the same box twice. The number of return errors within and between trials is recorded. The Purdue Pegboard (Gardner & Broman, 1979) bimanual task (number of pegs placed with both hands together) was selected as a measure of visuomotor ability and manual dexterity. For this task, children are asked to place as many pegs as possible into the board using both hands simultaneously within 30 seconds. The raw scores for each of these behavioral measures were obtained from the data repository for each child.

2.3 MRI Acquisition/Analysis and Measures

The NIH Study of Normal Brain Development collected whole brain MRI using 1.5T General Electric or Siemens Medical Scanners with 1.2 mm slice thickness, 1 mm in-plane resolution. T1-weighted images were acquired using an RF-spoiled gradient echo with a 22-25 ms repetition time, 10-11 ms echo time, 30° excitation angle, 180° refocusing pulse, and 256 anterior-posterior field of view. T2-weighted and proton-density weighted images were acquired using a fast/turbo spin echo, repetition time of 3500 ms, 90° excitation angle, effective echo time of 12-17 ms, and 256 mm anterior-posterior field of view. Centralized data processing performed on the data by the Brain Development Cooperative Group involved the following procedures: image corrections for image intensity non-uniformity, spatial normalization using Automated Non-linear Image Matching and Anatomical Labeling (ANIMAL), and tissue classification using Intensity-Normalized Stereotaxic Environment for Classification of Tissues (INSECT), and automatic surface parameterization (Constrained Laplacian-based Automated Segmentation with Proximities Algorithm - CLASP). The combination of ANIMAL, INSECT, and CLASP provided enhanced classification and segmentation of the pediatric volumes.

Consistent with the evidence regarding the neural substrates for the behavioral dependent measures of interest, the following segmented volumes (in cubic centimeters – cm^3) were obtained from the data repository for each child: 1) total gray matter, 2) total white matter, 3) frontal gray matter, 4) frontal white matter, 5) parietal gray matter, 6) parietal white matter, 7) cerebellum, 8) caudate, 9) putamen, and 10) globus pallidus.

2.4. Statistical Analysis

Previous studies have reported age and gender differences in these brain volumes (De Bellis et al., 2001; Lenroot et al., 2007; Reiss et al., 1996; Sowell et al., 2002) and behavioral measures (Waber et al., 2007). Thus, the brain volumes and behavioral measures were subjected to a two-level statistical analysis – the first to account for age and gender effects and the second to examine the relationships between the brain volumes and behavior above and beyond the first-level effects. For the first level analysis, we employed linear mixed effects modeling (also known as random effects models). This type of analysis is ideal for data sets consisting of multiple measurement points (i.e., repeated measures) with missing data and/or irregular intervals between measurements. This statistical approach is consistent with those employed in recent developmental investigations of longitudinal MRI data (Lenroot et al., 2007; Shaw et al., 2008; Tiemeier et al., 2010). Although higher order models (quadratic, cubic) were tested, linear models were most appropriate (parsimonious) for the age range examined presently (6.00 – 12.99 years). Thus, each dependent variable of interest was modeled as:

$$Y_{ij}=\beta_0+\beta_1 X_1+\beta_2 X_2+\gamma_i+\varepsilon_{ij}$$

where: Y_{ij}= observed MRI volume or behavioral variable for individual i at time j,

β_0,β_1, and β_2 = regression coefficients

X_1 *and* X_2 = age and gender

γ_i is the random intercept for subject *i*, with $\gamma_i \sim N(0, \sigma_r^2)$

ε_{ij} = residuals, with $\varepsilon_{ij} \sim N(0, \sigma^2)$, ε_{ij} and ε_{il} are independent.

In this equation β_0 is the intercept parameter. β_1 *and* β_2 are the slope parameters for age and gender, respectively. This model accounts for within-subject associations due to repeated observations from individuals contributing data at two measurement occasions, and were modeled using the random intercept γ_i. This model is equivalent to the linear mixed model with compound symmetric variance-covariance structure.

For the second level analysis, the residuals from each of the linear mixed models were obtained. Given that within-subject associations were controlled for in the first-level model, these conditional residuals are independent of within and between subject factor effects. These conditional residuals were analyzed using Pearson’s correlation to determine associations between the brain volumes and the behavioral (cognitive and motor) variables, above and beyond the effects of age and gender. For all analyses significance levels (*P* values) are provided in three categories ($P < 0.05$, $P < 0.01$, and $P < 0.001$).

3. Results

3.1. Validation of Age and Gender Effects on Cortical and Subcortical Volumes

Figure 1 depicts all brain volumes and behavioral variables of interest with respect to age and gender. Table 2 presents the coefficients (βs) from the first level model with respect to age and gender, as well as the *t* and *P* values for each measure. Consistent with previous research (Barnea-Goraly et al., 2005;Lenroot et al., 2007;Paus et al., 1999,Reiss et al., 1996), a significant positive relationship was found for age and the volume of total and frontal white matter, parietal white matter, and the cerebellum, while a significant negative relationship was found for parietal gray matter and age (Figure 1 and Table 2). Also consistent with previous literature (Waber et al., 2007) a significant positive relationship was found between age and full scale IQ as well as age and pegboard performance ($P < 0.001$ for both). No additional significant age effects were found for the other brain volumes or for spatial working memory ($P > 0.05$ for all).

Significant gender effects were found for all brain volumes ($P < 0.001$ for all), with the exception of the globus pallidus ($P > 0.05$). These results confirm previous reports that found that males exhibit greater volumes compared to females for these brain areas (Lenroot et al., 2007; Reiss et al., 1996). There were no significant gender effects for any behavioral variables ($P > 0.05$ for all).

3.2. Relationships between brain volume and cognitive-motor abilities above and beyond age and gender

In order to determine the unique relationships found between the brain volumes and cognitive-motor abilities, correlations among the residuals (based on the first level analysis accounting for age and gender) were examined. Table 3 depicts the correlations (correlation coefficients and associated significance levels) between the residual brain volumes and residual behavioral variables.

After accounting for age and gender in both the brain volumes and the behavioral variables, several significant relationships emerged. Specifically, residual full scale IQ was positively related to the residual volumes for total and frontal gray matter, parietal gray, cerebellum, and caudate. Residual IQ was also positively related to the residual pegboard scores. There was an inverse relationship between IQ and parietal white matter, as well as between IQ and spatial working memory (number of errors). In addition, spatial working memory was found positively related to the volume of the putamen.

4. Discussion

These results provide new evidence regarding the relationship between cognitive and motor functions at both the level of brain structure and behavior in typically developing children. By accounting for age and gender effects that have been previously reported in developmental MRI studies (De Bellis et al., 2001; Reiss et al., 1996; Sowell et al., 2002), we found significant relationships between general cognitive ability (IQ) and the volume of subcortical brain structures (cerebellum and caudate). These brain structures have been previously implicated in contributing to both cognitive and motor functions in adults and children with developmental disorders. In addition, IQ was found to be related to global and frontal gray matter volume as well as parietal gray and white matter. Moreover, general cognitive ability was also found to be related to visuomotor ability (pegboard) and executive function (spatial working memory). These results support the notion that cognition and motor skills may be fundamentally interrelated behaviorally and with regard to the underlying brain structures. If age and gender were not accounted for in the first-level statistical models, these relationships may have been otherwise obscured. Moreover, these results suggest that the relationships between cognitive ability and brain volume as well as the relationships among cognitive and motor abilities are already established by the age of 6, regardless of gender.

4.1. Age and Gender Differences in Global and Regional Brain Development

Consistent with previous studies, we found age-related increases in the volume of cortical structures including: total white matter, frontal white matter, and parietal white matter. With respect to cortical white matter development, the current age-related results are consistent with previous volumetric studies of typical brain development across a similar age range (Barnea-Goraly et al., 2005; Lenroot et al., 2007; Paus et al., 1999). These previous studies have attributed the increase in total white matter across age to greater volume of tracts such as the corpus callosum and posterior aspect of the internal capsule. Improvements in the speed and fidelity of neural transmissions due to myelination of these tracts are likely involved in the development of cognitive and motor abilities across childhood (Barnea-Goraly et al., 2005; Paus et al., 1999).

In addition to these age-related changes, gender differences were also found for all of the cortical brain volumes examined. These results are consistent with volumetric studies across childhood (De Bellis et al., 2001; Lenroot et al., 2007; Reiss et al., 1996; Sowell et al., 2002). In particular, Reiss and colleagues (2002) reported that males exhibit 11% and 7.5%

greater total gray and white matter volume, respectively. Moreover, regionally-specific differences were also reported by Lenroot and colleagues (2007) in which gender differences were evident in all lobar gray and white matter volumes examined. However, the functional implication and underlying mechanisms that result in gender differences remain unclear.

With respect to the age- and gender-related differences in subcortical volumes, the current results are consistent with Sowell et al. (2002), who found age-related differences in cerebellal volumes, and gender-related differences in both cerebellar and striatal volumes. More recently, Tiemeier and colleagues (2010) not only found age and gender effects in total cerebellar volume, but also found significant age and gender differences in the inferior posterior region of the cerebellar hemispheres. Importantly, this region of the cerebellum projects to the prefrontal and parietal regions of cortex and is likely associated with higher-order cognitive functions (Middleton & Strick, 1994). Although the volume of the cerebellum was not parsed into constituent regions in the present study, the current findings suggest that developmental changes in cerebellar volume may provide an important substrate for cognitive functions across childhood.

4.2. Cognitive Performance and Brain Volume

After accounting for age and gender, the volume of the cerebellum and caudate were found to be positively related to IQ. Similarly, the putamen was found to be related to executive function (spatial working memory). These results provide new evidence regarding the role of these subcortical structures in higher-order cognition for typically developing children and are consistent with previous studies in adults (Paradiso et al., 1997) and adolescents (Frangou et al., 2004). A recent study by Lange and colleagues (2010) examined the relationship between IQ and brain volumes across childhood, but did not find a significant association between IQ and subcortical volumes (including the cerebellum). In contrast, the current study revealed novel relationships between the caudate and cerebellum with IQ in school-aged children only after age and gender were accounted for in the statistical models. Moreover, the current results provide direct evidence for the relationship between the volume of the cerebellum and higher-order cognitive functions in typically developing children, a relationship that was proposed but not previously examined (Tiemeier et al., 2010).

The current findings also provide additional support for the relationship between the striatum (caudate and putamen) and higher-order cognitive functions (IQ and executive function, respectively). The relationship between IQ and the caudate has been reported in one volumetric study in children (Reiss et al., 1996) and is consistent with anatomical studies in non-human primates in which the caudate is involved in "cognitive" cortico-striatal loops and is linked to the dorsolateral prefrontal cortex (Alexander, DeLong, & Strick, 1986). However, the finding that the putamen volume is related to spatial working memory has not been previously reported in typically developing children. Moreover, this finding appears to be inconsistent with the notion that the putamen is involved in a "motor" cortico-striatal loop, interfacing with the supplementary motor cortex, premotor, primary motor cortex, and somatosensory cortex, and that this loop is distinct from its "cognitive" counterpart (Alexander, DeLong, & Strick, 1986). However, there is some new evidence from a resting state connectivity study in adults reporting significant positive correlations between the ventral rostral aspects of the putamen with rostral anterior cingulate (BA 32 and BA24) as well as the dorsolateral prefrontal cortex (BA 10) (Di Martino et al., 2008). Functional imaging studies have also reported putamen involvement in executive tasks comparing adults and children. For example, Bunge et al. (2002) found greater activation in the putamen in adults compared to children during No-Go trials and during an Eriksen Flanker task. Similarly, Rubia et al. (2006) also found greater putamen activation during

Switch tasks and Simon tasks in adults compared to children. Given that the putamen appears to contribute to components of executive function such as motor inhibition, task switching, and suppression of visual conflict, it is also likely that the putamen also contributes to working memory as in the current study. Thus, it does not appear appropriate to consider the putamen a strictly “motor” structure; the current study provides new support for the notion that the putamen may also contribute to non-motor functions.

In addition to these new subcortical findings, this study confirms relationships between IQ and cortical development (i.e., total and frontal gray matter) that have been previously reported (Shaw et al., 2006). Shaw and colleagues (2006) observed that children with superior intelligence experienced rapid cortical growth (greater cortical thickness) between 7 and 11 years, while children with average or low intelligence exhibited cortical thinning across this age range. Given that the majority of the children in the present study exhibit high or superior intelligence, the positive correlation between gray matter volume and IQ provide confirmatory evidence. The finding that parietal gray matter and parietal white matter are also related to IQ has not been found previously, but is consistent with the notion that the parietal lobe may interact with the frontal lobes during both cognitive and motor functions. Although the mechanisms underlying the changes in cortical development related to IQ are largely unknown, Shaw and colleagues (2006) attributed changes in cortical thickness to additional formation of usage-dependent synapses.

4.3. Overlapping Behavioral Trajectories of Cognitive and Visuomotor Development

Although the hypothesized relationships between visuomotor ability and brain volumes were not supported, this study sheds new light on the positive relationship between intelligence and visuomotor performance after accounting for the effects of age and gender. This finding supports the notion that cognitive and motor behaviors may be interrelated and potentially mutually influential in the continued development of these abilities across childhood. The relationship between cognitive and motor skills has been previously proposed (Diamond, 2000; Rosenbaum et al., 2001) and is strongly supported by extensive research at both the level of behavior and brain structures in children with developmental disorders. However, only recently has this relationship been examined in typically developing children, and only at the behavioral level (Davis et al., 2010; Martin et al., 2010; Wassenberg et al., 2005). The current study provides additional evidence that relationship found between visuomotor ability and cognition is also present in typically developing children using measures that have not been previously examined (Purdue Pegboard and WASI Full Scale IQ). Since this result emerges after accounting for age and gender, interestingly, it appears that the relationship is already established by 6 years of age regardless of gender. Thus, establishing a child’s trajectory for cognitive and motor skills at a very early age may have broad implications across these two domains and with respect to the child’s continued brain development. This would likely be the case for both typically developing children and for children with developmental disorders.

4.4. Conclusions and Translational Implications

Taken together, this study demonstrated that cognitive and motor functions are related at both the behavioral and neuroanatomical levels. Although the mechanisms underlying brain development across childhood remain largely unknown, the present results suggest that enriched cognitive or motor experiences may promote behavioral improvements *across* these two domains and may also influence the development of brain structures mediating these functions. Indeed, environmental factors such as engagement in physical and cognitive activities have been found to influence developmental plasticity across the lifespan, and particularly in older adults (Hillman et al., 2008; Kramer & Erickson, 2007; Hertzog et al, 2009). Longitudinal studies are necessary to investigate the efficacy of these types of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

enriched environments in typically developing children and those with developmental disorders. In particular, it would be interesting to determine if there is a differential effect of fitness (aerobic exercise) training in comparison to motor skill training on anatomical brain development in children with and without development disorders. This line of research would replicate the elegant animal work (Adkins, Boychuk, Remple, & Kleim, 2006; Black et al., 1990; Kleim et al., 1998) in humans and support the notion of experience-dependent neuronal plasticity mediating cognitive and motor functions in child development. Importantly, these studies are necessary to provide a foundation for different types of brain-based interventions in both typically developing and clinical populations that will have direct implications on academic achievement, physical health, and brain function.

A primary aim of the NIH Study of Normal Brain Development was the creation of developmental trajectories of brain volumes and behavioral performance in typically developing children, which would serve as a means for comparison to those with developmental disorders. One translational implication of the current study is to use these typically developing trajectories to determine if an individual clinical patient appears delayed (i.e., similar to younger typically developing children) or different (i.e., following an altogether different trajectory). Determining whether a patient is *developmentally delayed*, as opposed to *different*, is not possible if only age-matched controls are used in comparison to patients and may have drastic consequences on the way that a patient is diagnosed and treated. Moreover, these trajectories provide valuable information for longitudinal characterizations of individual patients' response to behavioral or pharmacological interventions. For example, it is possible to determine the extent to which an individual's deficits resolve (e.g., resemble his/her typically developing peers), remain delayed, or remain different.

4.5. Study Limitations & Future Directions

This study provides new evidence regarding the relationship between cognitive and motor functions at the level of the brain structure and behavior. However, there several limitations to the current study which may inform future directions in this research area. First, although puberty status was taken into consideration in the refinement of this dataset using the scores on the Puberty Development Scale, future studies will benefit from using both questionnaires of this type *and* assessments of hormone levels. This would ensure accurate characterization of children's puberty status and would provide evidence regarding the effects of hormonal changes on brain development and cognitive-motor behavior. Second, the MRI dataset available consisted of global and lobar volumes. It would be of interest in the future to examine functionally-relevant subregions within these volumes (e.g., dorsolateral prefrontal, anterior cingulate, premotor, primary motor, cerebellar hemispheres or vermis, etc.) and the connections between these subregions (e.g., using diffusion tensor imaging). In doing so, we may determine if cognitive and motor cortical-subcortical loops develop in parallel but with distinct trajectories or if these functional circuits interact across development. Third, given our primary interest in cognitive and motor abilities, future studies would benefit from the use of additional behavioral measures that assess specific aspect of executive control (e.g., Eriksen Flanker, Go-NoGo, Stroop, etc.) and detailed assessments of motor skill and coordination (e.g., The Movement Assessment Battery for Children (MABC) or the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP)). In particular, the use of tasks that assess higher-order motor skills, such as those requiring coordination between body/limb segments, goal-directed planning, precise timing, or motor inhibition may demonstrate even greater overlap with the development of cognitive/executive skills.

Research Highlights

1. Subcortical volumes are related to cognitive ability in school-age children.
2. Similar cortical neural substrates underlie cognitive and motor skills.
3. There is a relationship between cognitive and motor skills in typically-developing children.

Acknowledgments

The data set used in the preparation of this manuscript were obtained from the Pediatric MRI Data Repository (data release 2) created by the NIH MRI Study of Normal Brain Development. This multi-site, longitudinal study of typically developing children was conducted by the Brain Development Cooperative Group supported by the National Institute for Child Health and Human Development, National Institute on Drug Abuse, National Institute of Mental Health, and National Institutes of Neurological Disorders and Stroke - contract #s N01-HD023343, N01-MH90002, N01-NS92314, -2315, - 2316, -2317, -2319, -2320. This manuscript reflects the views of the authors and may not reflect the opinions or views of the Brain Development Cooperative Group Invesitators or the NIH. We would like to thank the Brain Development Cooperative Group for their work on the data collection and processing of the structural MRI. We would also like to thank Dr. Judith Rumsey for her assistance in accessing the data repository. Additional support for the current study was provided by a seed grant from the School of Public Health at the University of Maryland (to AJH) and NIH F31HD612102 (to MMP).

Reference List

Adkins DL, Boychuk J, Remple MS, Kleim JA. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. Journal of Applied Physiology. 2006; 101:1776–1782. [PubMed: 16959909]

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience. 1986; 9:357–381.

Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, et al. White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. Cerebral Cortex. 2005; 15:1848–1854. [PubMed: 15758200]

Black JE, Isaacs K, Anderson BJ, Alcantara AA, Greenough W. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proceedings of the National Academy of Sciences of the United States of America. 1990; 87:5568–5572. [PubMed: 1695380]

Evans AC. Brain Development Cooperative Group. The NIH MRI study of normal brain development. NeuroImage. 2006; 30:184–202. [PubMed: 16376577]

Bunge SA, Dudukovic NM, Thomason ME, Vaidya CJ, Gabrieli JDE. Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. Neuron. 2002; 33:301–311. [PubMed: 11804576]

Carper RA, Courchesne E. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain. 2000; 123:836–844. [PubMed: 10734014]

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA: The Journal of the American Medical Association. 2002; 288:1740–1748. [PubMed: 12365958]

CeNeS. Cambridge Neurological Test Automated Battery (Version 2.35). Cambridge, UK: CeNeS Cognition; 1998.

Davis AS, Pass LA, Finch WH, Dean RS, Woodcock RW. The canonical relationship between sensory-motor functioning and cognitive processing in children with attention-deficit/hyperactivity disorder. Archives of Clinical Neuropsychology. 2009; 24:273–286. [PubMed: 19574293]

Davis EE, Pitchford NJ, Jaspan T, McArthur D, Walker D. Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood. Cortex. 2010; 46:919–932. [PubMed: 20338554]

De Bellis MD, Keshavan MS, Beers SR, Hall J, Frustaci K, Masalehdan A, et al. Sex differences in brain maturation during childhood and adolescence. Cerebral Cortex. 2001; 11:552–557. [PubMed: 11375916]

Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Development. 2000; 71:44–56. [PubMed: 10836557]

Di Martino A, Scheres A, Margulies DS, Kelly AMC, Uddin LQ, Shehzad Z, et al. Functional connectivity of human striatum: A resting state fMRI study. Cerebral Cortex. 2008; 18:2735–2747. [PubMed: 18400794]

Eliasson A-C, Rosblad B, Forssberg H. Disturbances in programming goal-directed arm movements in children with ADHD. Developmental Medicine and Child Neurology. 2004; 46:19–27. [PubMed: 14974643]

Floyer-Lea A, Matthews PM. Changing brain networks for visuomotor control with increased movement automaticity. Journal of Neurophysiology. 2004; 92:2405–2412. [PubMed: 15381748]

Frangou S, Chitins X, Williams SCR. Mapping IQ and gray matter density in healthy young people. NeuroImage. 2004; 23:800–805. [PubMed: 15528081]

Fuentes CT, Mostofsky SH, Bastian AJ. Children with autism show specific handwriting impairments. Neurology. 2009; 73:1532–1537. [PubMed: 19901244]

Gardner RA, Broman M. The Purdue Pegboard: Normative Data on 1334 school children. Journal of Clinical Child Psychology. 1979; 8:156–162.

Gilger JW, Kaplan BJ. Atypical brain development: A conceptual framework for understanding developmental learning disabilities. Developmental Neuropsychology. 2001; 2(2):465–481. [PubMed: 11892948]

Hertzog C, Kramer AK, Wilson RS, Lindenberger U. Enrichment effects on adult cognitive development: Can functional capacity of older adults be preserved and enhanced? Psychological Science in the Public Interest. 2009; 9:1–65.

Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nature Reviews: Neuroscience. 2008; 9:58–65.

Hughes C. Brief report: Planning problems in autism at the level of motor control. Journal of Autism & Developmental Disorders. 1996; 26:99–107. [PubMed: 8819773]

Kaplan BJ, Wilson BN, Dewey D, Crawford SG. DCD may not be a discrete disorder. Human Movement Science. 1998; 17:471–490.

Kleim JA, Swain RA, Armstrong KA, Napper RM, Jones TA, Greenough WT. Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. Neurobiology of Learning and Memory. 1998; 69:274–289. [PubMed: 9707490]

Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends in Cognitive Sciences. 2007; 11:342–34. [PubMed: 17629545]

Lange N, Froimowitz MP, Bigler ED, Lainhart JE. Associations between IQ, total and regional brain volumes, and demography in a large normative sample of healthy children and adolescents. Developmental Neuropsychology. 2010; 35:296–317. [PubMed: 20446134]

Langen M, Schnack HG, Nederveen H, Bos D, Lahuis BE, de Jonge MV, et al. Changes in the developmental trajectories of striatum in autism. Biological Psychiatry. 2009; 66:327–333. [PubMed: 19423078]

Leary MR, Hill DA. Moving on: autism and movement disturbance. Mental Retardation. 1996; 34:39–53. [PubMed: 8822025]

Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage. 2007; 36:1065–1073. [PubMed: 17513132]

Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, Minshew NJ, et al. Maturation of widely distributed brain function subserves cognitive development. NeuroImage. 2001; 13:786–793. [PubMed: 11304075]

Martin R, Tigera C, Denckla MB, Mahone EM. Factor structure of paediatric timed motor examination and its relationship with IQ. Developmental Medicine and Child Neurology. 2010; 52:e188–e194. [PubMed: 20412260]

McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, et al. Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain. 2005; 128:268–276. [PubMed: 15548557]

Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science. 1994; 266:458–461. [PubMed: 7939688]

Miyahara M, Tsujii M, Hori M, Nakanishi K, Kageyama H, Sugiyama T. Brief report: Motor incoordination in children with asperger syndrome and learning disabilities. Journal of Autism and Developmental Disorders. 1997; 27:595–603. [PubMed: 9403374]

Mostofsky SH, Reiss AL, Lockhart P, Denckla MB. Evaluation of cerebellar size in attention-deficit hyperactivity disorder. Journal of Child Neurology. 1998; 13:434–439. [PubMed: 9733289]

Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2002; 52:785–794. [PubMed: 12372650]

Paradiso S, Andreasen NC, O'Leary DS, Arndt S, Robinson RG. Cerebellar size and cognition: correlations with IQ, verbal memory and motor dexterity. Neuropsychiatry, Neuropsychology, and Behavioral Neurology. 1997; 10:1–8.

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. Science. 1999; 283:1908–1911. [PubMed: 10082463]

Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. Journal of Youth and Adolescence. 1988; 17:117–133.

Piek JP, Dyck MJ. Sensory-motor deficits in children with developmental coordination disorder, attention deficit hyperactivity disorder, and autistic disorder. Human Movement Science. 2004; 23(3-4):475–488. [PubMed: 15541530]

Piek JP, Dyck MJ, Nieman A, Anderson M, Hay D, Smith LM, et al. The relationship between motor coordination, executive functioning and attention in school aged children. Archives of Clinical Neuropsychology. 2004; 19:1063–1076. [PubMed: 15533697]

Pitcher TM, Piek JP, Hay DA. Fine and gross motor ability in males with ADHD. Developmental Medicine & Child Neurology. 2003; 45:525–535. [PubMed: 12882531]

Qiu A, Crocetti D, Adler M, Mahone EM, Denckla MB, Miller MI, et al. Basal ganglia volume and shape in children with attention deficit hyperactivity disorder. American Journal of Psychiatry. 2009; 166:74–82. [PubMed: 19015232]

Querne L, Berquin P, Vernier-Hauvette MP, Fall S, Deltour L, Meyer ME, et al. Dysfunction of the attentional brain network in children with Developmental Coordination Disorder: A fMRI study. Brain Research. 2008; 1244:89–102. [PubMed: 18718456]

Racine MB, Majnemer A, Shevell M, Snider L. Handwriting performance in children with attention deficit hyperactivity disorder (ADHD). Journal of Child Neurology. 2008; 23:399–406. [PubMed: 18401033]

Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB. Brain development, gender and IQ in children: A volumetric imaging study. Brain. 1996; 119:1763–1774. [PubMed: 8931596]

Rinehart N, Bradshaw J, Brereton A, Tonge B. Movement preparation in high-functioning autism and asperger disorder: A serial choice reaction time task involving motor reprogramming. Journal of Autism and Developmental Disorders. 2001; 31:79–88. [PubMed: 11439757]

Rosenbaum DA, Carlson RA, Gilmore RO. Acquisition of intellectual and perceptual-motor skills. Annual Review of Psychology. 2001; 52:453–70.

Rubia K, Smith AB, Taylor E, Brammer M. Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. Human Brain Mapping. 2007; 28:1163–1177. [PubMed: 17538951]

Rubia K, Smith AB, Woolley J, Nosarti C, Heyman I, Taylor E, et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Human Brain Mapping. 2006; 27:973–993. [PubMed: 16683265]

Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, et al. Intellectual ability and cortical development in children and adolescents. Nature. 2006; 440:676–679. [PubMed: 16572172]

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopmental trajectories of the human cerebral cortex. Journal of Neuroscience. 2008; 28:3586–3594. [PubMed: 18385317]

Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Developmental Medicine and Child Neurology. 2002; 44:4–16. [PubMed: 11811649]

Staines WR, Padilla M, Knight RT. Frontal-parietal event-related potential changes associated with practising a novel visuomotor task. Cognitive Brain Research. 2002; 13:195–202. [PubMed: 11958962]

Tiemeier H, Lenroot RK, Greenstein DK, Tran L, Pierson R, Giedd JN. Cerebellum development during childhood and adolescence: A longitudinal morphometric MRI study. NeuroImage. 2010; 49:63–70. [PubMed: 19683586]

Waber DP, De Moor C, Forbes PW, Almli CR, Botteron KN, Leonard G, et al. The NIH MRI study of normal brain development: Performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. Journal of the International Neuropsychological Society. 2007; 13:729–746. [PubMed: 17511896]

Wassenberg R, Feron FJM, Kessels AGH, Hendriksen JGM, Kalff AC, Kroes M, et al. Relation between cognitive and motor performance in 5- to 6-year-old children: Results from a large-scale cross-sectional study. Child Development. 2005; 76:1092–1103. [PubMed: 16150004]

Wechsler, D. Wechsler Abbreviated Scales of Intelligence. New York: Psychological Corporation; 1999.

Wilke M, Sohn JH, Byars AW, Holland SK. Bright spots: correlations of gray matter volume with IQ in a normal pediatric population. Neuroimage. 2003; 20:202–215. [PubMed: 14527581]

Zwicker JG, Missiuna C, Boyd LA. Neural correlates of developmental coordination disorder: A review of hypotheses. Journal of Child Neurology. 2009; 24:1273–1281. [PubMed: 19687388]

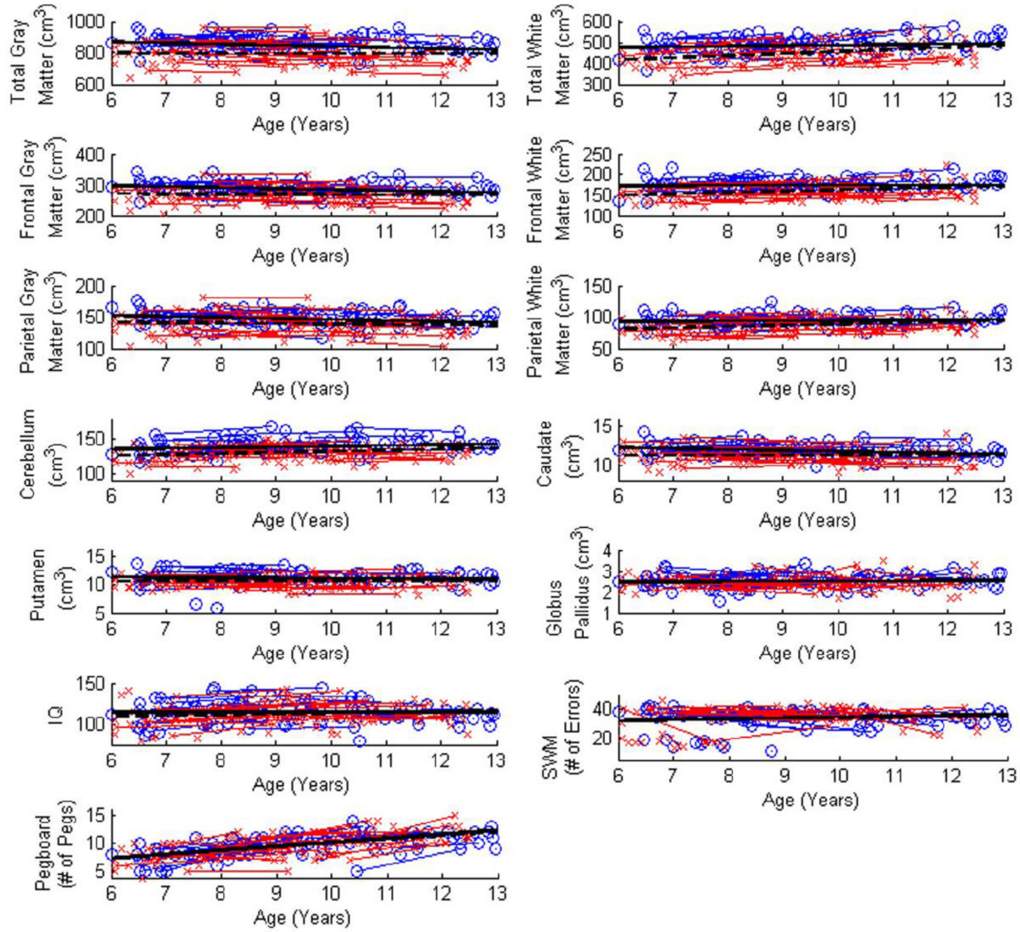

Figure 1.

Scatter plots of the brain volumes and behavioral variables with respect to age and gender. Males are depicted as blue circles and females as red crosses. Individuals with two data points are connected with lines (blue for males and red for females). The linear fits for each gender are presented as heavy black lines (solid for males and dashed for females).

Table 1

Sample descriptors. Means are presented with standard deviations in parentheses.

	One Measurement Occasion Only Measurement Occasion 1 or 2		Two Measurement Occasions			
			Measurement Occasion 1		Measurement Occasion 2	
Gender	Males (N = 49)	Females (N = 78)	Males (N = 19)	Females (N = 26)	Males (N = 19)	Females (N = 26)
Age (Years)	9.52 (2.05)	9.33 (1.87)	8.00 (1.36)	8.10 (1.36)	9.93 (1.39)	9.98 (1.34)
Full Scale IQ	111.35 (13.13)	109.97 (13.87)	115.32 (14.31)	113.31 (11.67)	120.42 (13.17)	117.42 (13.04)
Spatial Working Memory (# Errors)	31.86 (8.25)	32.99 (7.97)	36.32 (3.18)	33.58 (11.09)	33.58 (4.8)	34.96 (5.39)
Pegboard (# Pegs Both Hands)	9.53 (1.86)	9.77 (1.95)	8.00 (1.89)	8.65 (1.77)	10.53 (1.39)	10.31 (2.29)
Total Gray Matter Volume (cm^3)	851.31 (55.19)	774.27 (62.15)	861.49 (42.68)	803.87 (74.40)	860.41 (44.67)	802.67 (76.79)
Total White Matter Volume (cm^3)	492.70 (56.27)	438.59 (48.65)	482.05 (28.79)	432.06 (45.17)	506.23 (38.83)	450.39 (46.85)
Frontal Gray Matter Volume (cm^3)	289.70 (22.18)	261.48 (21.95)	290.85 (18.54)	271.61 (26.35)	290.53 (19.24)	272.05 (27.38)
Frontal White Matter Volume (cm^3)	177.01 (22.02)	156.76 (18.48)	173.19 (11.89)	154.46 (16.35)	182.12 (14.65)	161.40 (17.38)
Parietal Gray Matter Volume (cm^3)	149.05 (13.04)	136.21 (14.15)	150.38 (9.61)	142.64 (17.05)	147.00 (11.55)	140.61 (17.45)
Parietal White Matter Volume (cm^3)	95.94 (11.06)	85.02 (11.34)	93.40 (7.68)	85.11 (11.71)	97.61 (8.17)	88.47 (11.09)
Cerebellum Matter Volume (cm^3)	138.64 (10.46)	127.46 (11.68)	140.73 (11.48)	130.05 (8.98)	145.38 (10.81)	132.87 (10.02)
Caudate Volume (cm^3)	11.68 (0.92)	10.94 (0.98)	12.15 (0.67)	11.33 (1.03)	12.25 (0.73)	11.38 (1.02)
Putamen Volume (cm^3)	11.03 (1.45)	10.35 (1.02)	11.57 (1.03)	10.42 (0.99)	11.59 (0.89)	10.47 (0.97)
Globus Pallidus (cm^3)	2.47 (0.32)	2.52 (0.34)	2.52 (0.35)	2.48 (0.29)	2.75 (0.29)	2.43 (0.30)

Table 2

First level mixed model output (coefficients, t statistics, and P values) for each behavioral and brain measure.

	Intercept (β_0)		Age (β_1)		Gender (β_2)	
	Coefficient (SE)	***t (DOF)***	**Coefficient (SE)**	***t (DOF)***	**Coefficient (SE)**	***t (DOF)***
Full Scale IQ	100.61 (3.99)	t (170) = 25.21***	1.35 (0.39)	t (44) = 3.48**	-1.72 (2.14)	t (44) = -0.81
Spatial Working Memory (# Errors)	28.48 (2.59)	t (170) = 10.99***	0.48 (0.26)	t (44) = 1.80	0.90 (1.06)	t (44) = 0.84
Pegboard (# Pegs Both Hands)	2.83 (0.58)	t (170) = 4.97***	0.71 (0.06)	t (44) = 12.12***	0.30 (0.24)	t (44) = 0.21
Total Gray Matter Volume (cm^3)	870.58 (17.60)	t (170) = 49.48***	-1.76 (1.71)	t (44) = -1.03	-72.46 (9.48)	t (44) = -7.64***
Total White Matter Volume (cm^3)	404.35 (13.05)	t (170) = 30.99***	9.49 (1.25)	t (44) = 7.56***	-52.84 (7.32)	t (44) = -7.21***
Frontal Gray Matter Volume (cm^3)	294.95 (5.82)	t (170) = 50.67***	-0.53 (0.55)	t (44) = -0.97	-25.90(3.51)	t (44) = -7.38***
Frontal White Matter Volume (cm^3)	143.57 (4.44)	t (170) = 32.35***	3.59 (0.41)	t (44) = 8.75***	-19.76 (2.86)	t (44) = -6.91***
Parietal Gray Matter Volume (cm^3)	160.19 (4.00)	t (170) = 40.09***	-1.20 (0.39)	t (44) = -3.10**	-11.45 (2.17)	t (44) = -5.29***
Parietal White Matter Volume (cm^3)	79.51 (2.87)	t (170) = 27.73***	1.74 (0.27)	t (44) = 6.35***	-10.15 (1.65)	t (44) = -6.17***
Cerebellum Volume (cm^3)	123.31 (2.44)	t (170) = 50.47***	1.77 (0.22)	t (44) = 8.04***	-11.22 (1.69)	t (44) = -6.65***
Caudate Volume (cm^3)	11.72 (0.23)	t (170) = 50.08***	0.01 (0.02)	t (44) = 0.54	-0.78 (0.15)	t (44) = -5.20***
Putamen Volume (cm^3)	11.13 (0.29)	t (170) = 38.23***	0.00 (0.03)	t (44) = 0.22	-0.81 (0.17)	t (44) = -4.53***
Globus Pallidus (cm^3)	2.50 (0.12)	t (170) = 21.14***	0.00 (0.05)	t (44) = 0.36	-0.05 (0.05)	t (44) = -1.16

* Significance is indicated as $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$.

SE = Standard Error. DOF = Degrees of Freedom.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Correlations among residual brain volumes and residual behavioral variables (after accounting for age and gender). Correlation coefficients are presented with the associated significance level.

	Full Scale IQ	Spatial Working Memory (# of Errors)	Pegboard (# of Pegs Inserted)
Total Gray Matter	0.27***	-0.05	0.01
Total White Matter	-0.12	0.06	0.07
Frontal Gray Matter	0.21*	-0.05	-0.04
Frontal White Matter	-0.11	0.03	0.02
Parietal Gray Matter	0.15*	0.02	0.02
Parietal White Matter	-0.15*	0.04	0.03
Cerebellum	0.29***	0.04	0.06
Caudate	0.26***	0.05	0.09
Putamen	0.03	0.15*	-0.03
Full Scale IQ	1	-0.14*	0.27***
Spatial Working Memory	-0.14*	1	-0.12
Pegboard	0.27***	-0.12	1

*Significance is indicated as $p<0.05$,

** $p< 0.01$,

*** $p < 0.001$.

All brain variables are in units of cm^3.