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White matter integrity and cognitive performance in children with prenatal methamphetamine exposure

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Abstract

There is emerging evidence on the harmful effects of prenatal methamphetamine (MA) exposure on the structure and function of the developing brain. However, few studies have assessed white matter structural integrity in the presence of prenatal MA exposure, and results are inconsistent. This investigation thus used diffusion tensor imaging (DTI) to investigate white matter microstructure and cognitive performance in a group of prenatal MA exposed (or MA) children and controls of similar age. Seventeen MA children and 15 healthy controls (aged 6–7 years) underwent DTI and assessment of motor function and general cognitive ability. Whole brain analyses of white matter structure were performed using FSL's tract-based spatial statistics comparing fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). Mean diffusion values were extracted from white matter regions shown to differ across groups to determine whether variations in FA predicted cognitive performance. Analyses were controlled for maternal nicotine use. MA children showed significantly lower FA as well as higher MD, RD and AD in tracts that traverse striatal, limbic and frontal regions. Abnormal FA levels in MA children were significantly associated with poorer motor coordination and general cognitive ability sub-items that relate to aspects of executive function.Our findings suggest that, consistent with previous studies in older children, there are disruptions of white matter microstructural integrity in striatal, limbic and frontal regions of young MA exposed children, with prominent cognitive implications. Future longitudinal studies may clarify how prenatal MA exposure affects white matter structural connectivity at different stages of brain maturation.

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Disclosures

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Keywords

Prenatal; Methamphetamine; Diffusion tensor imaging; Cognitive function; Development

1. Introduction

The rising prevalence of methamphetamine (MA) use in pregnant women (USA: 8% in 1994 to 24% in 2006) means that, in recent years, an increasing number of children have been exposed to MA prenatally [1]. Animal studies and human brain imaging studies have demonstrated that prenatal MA exposure alters brain structure, metabolism and function, particularly in the striatum and temporal lobe, but also in frontal and parietal regions [2–4]. Further, structural changes in prenatal MA exposed (or MA) children have been associated with cognitive impairment in the domains of motor function (specifically visual-motor integration), executive function, memory and attention [5,6].

A few studies have investigated white matter microstructural integrity in MA children using diffusion tensor imaging (DTI). DTI determines water diffusion along white matter tracts by a number of metrics. Fractional anisotropy (FA) is a measure of diffusion directionality, where lower FA suggests reduced white matter integrity and myelination [7]. Mean diffusivity (MD) represents a global average of diffusion directions, which is higher when there are damaged and/or disorganized white matter tracts [8]. Radial diffusivity (RD) specifically reflects perpendicular diffusion towards membranes; RD is higher when there is less or damaged myelination [9,10]. Axial diffusivity (AD) specifically measures diffusion along axons, which is suggested to be increased when neurofilaments are damaged [11] or decreased when there is axonal damage [12,13].

Though abnormalities in the external capsule, and in the frontal and parietal white matter, are reported in more than one DTI study in MA children [14,15] regional inconsistences exist. For example, although Colby et al. [15] reported higher fractional anisotropy (FA) in left hemisphere cerebral white matter in MA children aged 7–13 years, lower FA in the right external capsule was associated with impaired visual-motor integration in MA children and controls. In turn, lower FA has been found in central, inferior and posterior brain regions in children aged 8–14 years who were exposed prenatally to opiates and other substances, including amphetamines [16].

Inconsistencies in the literature may be due to changes in brain development over time and the window in which these effects are investigated. Longitudinal changes in typically developing children appear to follow a pattern of linear increases in white matter volume from young childhood to adolescence [17]. Likewise, the direction of DTI parameters has been found to differ at different ages in frontal and parietal regions [18]. Colby et al. [15] reported higher FA in MA children that is opposite to previously reported lower FA levels in adults who used methamphetamine (e.g. Alicata et al. [19]). Hence, to better characterize brain insults related to prenatal MA exposure, researchers need to study children in a narrow age range.

Additional limitations of prior studies have included use of relatively coarse measurement methods and lack of controlling for potentially important confounders such as gender, nicotine, and comorbid drug use. Gender differences and prenatal nicotine exposure have been found to alter brain structure in children [20–22].

To help clarify and expand upon previous findings, the aim of this study was to investigate, in a sample of MA children with a narrow age range (6–7 years), white matter microstructural integrity using DTI, and its associations with cognitive performance. We included a group of controls matched on socioeconomic background, age and gender, and factored into our statistical analyses gender and nicotine use. At age 6–7 years, children in South Africa enter formal schooling; hence, affected children may exhibit accentuated structural abnormalities which could be associated with learning difficulties. There is particularly high prevalence of use in South Africa, e.g. 92% of mixed race women in a high risk local community have used MA during pregnancy [23]. Though previous findings are somewhat mixed, we hypothesised that MA children would have altered white matter integrity in striatal, temporal and frontal regions compared to controls, and that such alterations would be associated with impaired cognitive function in the domains of motor function and general cognitive ability including aspects of executive function.

2. Method

2.1. Subjects

Children aged 6–7 years residing in Cape Town, South Africa were recruited from a local school and care centre by means of telephonic interviews with teachers and mothers/caregivers. Children with and without prenatal MA exposure were matched on socioeconomic background, age and gender. All potential cases and controls were identified with assistance from the school and resident social worker. Subsequently, mothers/caregivers were contacted by a research assistant with help from the school, to verify information and invite families for participation. Children were excluded from participation if there was a history of genetic anomalies, neurological disorders, head injury or prematurity (less than 36 weeks gestation). The parent or legal guardian and child gave written consent or assent, respectively, for participation in the study. The study was approved by the Human Research Ethics Committee at the University of Cape Town and Stellenbosch University, and was conducted according to the ethical guidelines set out in the International Declaration of Helsinki 2008.

2.2. Procedures

Background information was verified at the first visit, before commencement of brain imaging. Information was gathered of the mother and child about demographic (e.g. age, gender, home language, and educational attainment), socioeconomic (e.g. income), and medical history (e.g. health history, gestation period, and birth weight), and verified by clinical records as applicable. Mothers/caregivers were also asked about cigarette smoking, alcohol use and/or other illicit drug use during pregnancy. We used the timeline follow-back method, a valid and reliable means of gathering retrospective data on the duration,

frequency, and severity of alcohol and drug exposure during pregnancy [24]. Anthropometric data including weight, length and head circumference of the child was also collected.

Children underwent diffusion tensor imaging using a Siemens Allegra 3 T MRI scanner while watching an animated movie. A special navigator motion-corrected sequence was used to acquire two diffusion-weighted images with phases in the anterior-posterior and posterior-anterior encoding directions [25]. Each image was acquired on a single channel head coil in axial orientation with the following parameters: 30 diffusion directions at $b = 1000$ mm/s^2 and $b = 0$ mm/s^2; repetition time [TR] = 7900 ms; echo time [TE] = 86 ms; FOV = 230 mm; flip angle = 0°; 20% distance factor and slice thickness of 2 mm; voxel size: 2.1 mm × 2.1 mm × 2.0 mm.

The Beery Developmental Test of Visual-Motor Integration (VMI) [26] was used to assess visual-motor integration, including aspects of visual perception (VMI VIS) and motor coordination (VMI MOT). The Grooved Pegboard Test (GPT) [27] was used to assess visual-motor coordination (time taken to insert pegs into holes on a pegboard with the dominant hand, and then the non-dominant hand). The Nonverbal Scale of the Kaufman Assessment Battery for Children-II (K-ABC-II) [28] was used to assess general cognitive ability that includes aspects of executive function and memory. The Nonverbal Scale of the K-ABC-II is preferred when language and cultural factors are likely to impact outcomes. Our sample was mainly Afrikaans-speaking and was of mixed race. The scale includes the Conceptual Thinking, Story Completion, Triangles, Block Counting, Pattern Reasoning, and Hand Movements subtests. Specifically, Conceptual Thinking assesses classification and induction ability; Story Completion assesses induction, visualization, and general sequential reasoning; Triangles evaluates spatial relations and visualization; Block Counting assesses conceptualisation and visualisation; Pattern Reasoning assesses induction and visualisation abilities; and Hand Movements assesses sequential processing and visual-spatial working memory. To these items we added the K-ABC-II Atlantis and Atlantis Delayed subtests; these were used to assess associative memory and delayed memory [29]. The Boston Naming Test (South African Short Form, BNT-SA-SF), based on the original 60-item BNT, was used to assess confrontation naming ability [30]. All these tests have been validated for use in children [8,31–33].

2.3. Data processing and analyses

Using Statistica 12, independent-sample t-tests, analyses of variance (ANOVA) and chi-square tests investigated between-group differences in sociodemographic and anthropometric variables. To prepare DTI data, scan volumes that were re-acquired due to movement as registered by the motion navigator during imaging were removed and the raw data visually inspected to remove further volumes with significant movement or other artefacts. A minimum of 12 volumes were retained. DTI pre-processing and analyses used the FMRIB Software Library (FSL) v 5.0 and previously validated tract-based spatial statistics (TBSS) [34]. In brief, data first underwent eddy current correction and then AP and PA images were corrected for susceptibility artefacts and merged using FSL topup. Subsequently, FA images were created by fitting a linear tensor model to the raw diffusion data. Brain extraction was performed using the FMRIB Software Library brain extraction

tool (FSL BET) [35] and FA data aligned into MNI space using the non-linear registration tool FNIRT [36,37]. A mean FA skeleton was created, representing the centre of the white matter tracts for each subject. Individually aligned FA data were mapped on the skeleton and projection transformations were applied to MD, AD and RD data.

Whole-brain group differences in DTI parameters were investigated using FSL randomise that employs a general linear model [38], at 5000 permutations per test at a threshold of 0.2, controlled for gender and nicotine use. Analyses were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) [39]. White matter regions were identified using the International Consortium of Brain Mapping (ICBM) DTI-81 white-matter atlas [40]. Anatomical regions surrounding white matter tracts were identified using the Harvard cortical and subcortical structural atlases [41]. Regions of interest (ROIs) were extracted by utilising the ICBM-DTI-81 white matter atlas for mask creation and subsequent estimation of mean values for DTI parameters.

These values were exported to Statistica 12 to investigate associations of diffusion parameters with cognitive data. Cognitive data including total scores and individual item scores were transformed to age-adjusted scaled scores for analyses. Multiple regression analyses determined whether FA levels in tracts found to differ significantly by group were associated with individual cognitive test scores. Tests were two-tailed and excluded scores outside the 95% confidence interval.

3. Results

Demographic information, anthropometric data and statistics of relevant group comparisons are shown in Table 1. The sample included 17 MA children and 15 healthy controls. Regarding anthropometric variables and maternal level of education, there were no significant between-group differences. However, mothers of MA children had higher rates of unemployment (75%) compared to control mothers (47%).

A significantly higher number of MA mothers (81%) than control mothers (40%) smoked [$\chi^2 = 5.55$, $p = 0.020$]. A small minority of MA mothers used alcohol during pregnancy (18%), but this was not significantly different from control mothers [$\chi^2 = 2.92$, $p = 0.087$]. ANOVAs used to quantify independent effects of smoking status and gender on FA showed that smoking status was significantly associated with lower FA in the right external capsule of MA children [$F(3,16) = 6.96$, $p = 0.006$].

MA children had significantly lower FA in the left external capsule, fornix and stria terminalis compared to controls, while controlling for gender and prenatal nicotine exposure (Table 2, Fig. 1). These tracts traversed striatal, limbic and frontal regions. MA children also had higher MD and RD in corresponding regions compared to controls. In addition, AD in the left sagittal stratum was significantly higher in the MA group. This tract includes the inferior fronto-occipital and inferior longitudinal fascicule.

Altered FA in the external capsule, sagittal stratum, and fornix/stria terminalis was significantly associated with poorer performance on some tests of motor coordination, and general cognitive ability that relate to aspects of executive function, in MA children

compared to controls (Table 3). Although the K-ABC determines general cognitive ability, sub-items (see Section 2.2) arguably assess aspects of executive function. Therefore, since there was no significant association between the general cognitive ability score and FA, and because this population may be more inclined to executive cognitive impairments due to frontal striatal involvement [5,6], associations of individual item scores were also considered. In addition, there was a trend for lower FA in the right external capsule to predict poorer motor coordination (as assessed by the VMI MOT, $p = 0.07$) in MA children.

4. Discussion

This investigation sought to characterize the effects of prenatal MA exposure on white matter microstructure and associated cognitive performance in young children (6–7 years of age). In MA children compared to controls, we observed (1) significantly lower FA, as well as higher MD, RD and AD in the external capsule, sagittal stratum, and fornix/stria terminalis, i.e. tracts that traverse striatal, limbic and frontal regions; and we found that (2) altered FA in these tracts was associated with poorer motor coordination and general cognitive ability including sub-items that relate to executive function.

There is a good deal of consistency in the literature regarding the neuroanatomical circuits that connect the regions implicated in the current study. Striatal and frontal regions are interconnected via the external capsule and by association fibres of the sagittal stratum [42,43]. The sagittal stratum includes different bundles of association fibres from the posterior temporal and occipital lobes, i.e. the inferior fronto-occipital and inferior and superior longitudinal fascicule. The fornix/stria terminalis represent limbic fibres that connect the hippocampus, amygdala and hypothalamus [43]. Our findings are similar to Colby et al. [15] with respect to location of affected white matter tracts, including the external capsule and sagittal stratum. Our findings are also consistent, at first glance, with studies that investigated the effects of MA use in adults, i.e. we also found lower FA and higher mean diffusivity in the striatum and frontal white matter [19,44].

Notably, the same white matter tracts showed differences in FA as well as MD in exposed children, suggesting that lower FA appears to be attributable to higher MD that indicates altered myelination [8]. The finding of higher RD that was evident again in the same tracts, underscore apparently inefficient myelination [10] in MA children. It appears that white matter structure is affected at a number of levels by exposure to MA in utero.

Furthermore, AD is expected to be lower with neural pathology or other insults that damage axons [12,13]. However, it appears that opposite patterns of AD occur in development, which possibly reflects structural changes including impaired neurofilaments inside axons [11]. The changes in AD observed here are consistent with studies reporting higher AD in white matter tracts of MA children [15] and children with attention-deficit/hyperactivity disorder compared to controls [45].

There is some inconsistency in the literature regarding directionality of diffusion parameters in studies of MA children. We found lower FA, and higher MD and RD, but other groups found the opposite in these metrics [14,15]. One explanation for this inconsistency may lie

in differing methodologies. For instance, whereas Cloak et al. [14] used the apparent diffusion coefficient to measure mean diffusion, we used the mean diffusivity metric. Another explanation may involve developmental adaptations in white matter structural integrity over time. Our study focused on a narrow age range of 6–7 years; in contrast, previous studies have used younger children (3–4 years) and older children across a wide age range (7–13 years).

Altered integrity of white matter tracts in substance exposed children could also relate to abnormally higher volumes of structures such as the striatum. A large structural MRI study on longitudinal volumetric changes in prenatal substance exposed children found atypically higher volumes of the posterior temporal lobe (to which the putamen extends) in children aged 5–7 years [17]. Similarly, we have previously found putamen volume increases in children of roughly the same age [21]. The data presented here was gathered in the same sample where we found this volume increase. Affected white matter tracts reported here principally traversed the putamen, which suggests that striatal structure is affected in more ways than one. Altered gray and white matter structure may be associated with less plasticity and suboptimal pruning of synapses in substance exposed children compared to healthy children [17].

Evidence of the functional significance of these alterations to microstructure integrity (especially in the striatum) is provided by our data showing that deficits in both motor coordination and higher-order cognitive ability were associated with alterations in DTI parameters. Note that supposed reformation of brain circuitry may explain why diffusion directionality varies across tracts and in relation to cognitive function; the structural connectivity of one network may be strengthened at the expense of efficiency in other networks (e.g. Roussotte et al. [46]). Higher FA in the right external capsule was associated with poorer visual-motor coordination (as measured by performance on the Grooved Pegboard Test) in MA children, although this finding needs to be confirmed in larger samples. There was also a trend for lower FA in the right external capsule to predict poorer performance on the Beery VMI, a result consistent with evidence from a group of MA, alcohol exposed and control children studied previously [15]. Furthermore, FA levels that varied by region (including the right external capsule, left sagittal stratum and left fornix/stria terminalis) was associated with performance in K-ABC items measuring various aspects of cognitive ability including executive function. Efficient motor coordination and executive function require effective integration amongst brain regions, e.g. the external capsule relays fibres of the sagittal stratum from the frontal and temporal lobes to the cerebral cortex [43]. The changes in FA and functional impairment in MA children are thus consistent with previous evidence of lower FA in the sagittal stratum of children aged 7–8 years who are visually-perceptually impaired [47], and associations of lower FA in the fornix with poorer associative learning in traumatic brain injury [48]. Functional effects of reformed trajectories may be particularly evident during certain age brackets when there are formal learning demands, e.g. upon entering school at age 6–7 years.

The principal involvement of the striatum is consistent with hypotheses regarding the primary target for neurotoxicity of MA on the brain. This focus is probably due to high dopamine receptor density in that brain region [49,50]. Based on findings using rodent

models, MA is postulated to cause increased catecholamine transmitter concentrations, including dopamine and noradrenalin, to levels where they metabolise to free radicals and result in loss of terminals due to oxidative damage [51]. MA has extensive neurotoxic effects on the serotonergic system, causing synaptic remodelling of axonal terminals across the brain [52]. In development, evidence from rodent models suggests that MA causes oxidative damage to synapses of neurons (in the striatum, amongst other regions), which leads to fetal reprogramming of the hypothalamic-pituitary-adrenal axis and of DNA [51,53]. Putatively, prenatal MA-exposure may cause similar oxidative damage to synapses in humans that affect white matter integrity particularly of the striatum, and cognitive function in children.

Limitations of this study included inability to accurately quantify maternal MA use and to clarify timing of its use in pregnancy. Selective disclosure and polysubstance use almost always confound studies of prenatal substance abuse. On the other hand, we were able to control for important potential confounding variables, including prenatal nicotine use, in our analyses. Although the sample size was small, groups were well matched and children were from the same ethnic background and socio-economic status.

Our findings suggest that, consistent with previous studies in older children, there are disruptions of white matter microstructural integrity in striatal, limbic and frontal regions of young MA children. These abnormalities are associated with impairment in motor coordination and general cognitive ability pertaining to aspects of executive function. Future longitudinal studies may clarify how prenatal MA exposure affects white matter structural connectivity at different stages of brain maturation.

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HIGHLIGHTS

- White matter microstructural integrity is disrupted in prenatal methamphetamine (MA) exposed children.
- White matter impairment coincides with impairment in motor function and aspects of executive function.
- Brain developmental trajectories may be altered due to MA exposure.

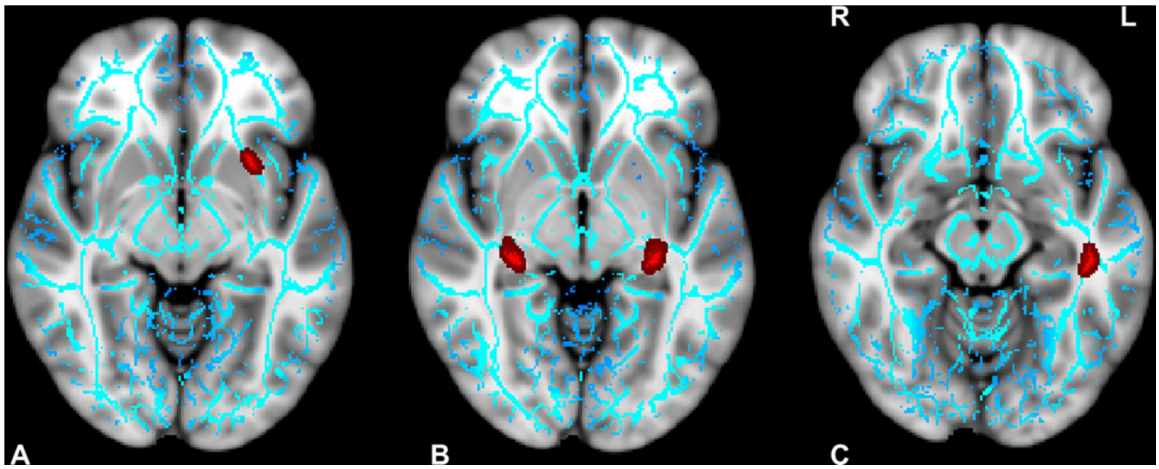

Fig. 1.

Significantly lower fractional anisotropy (FA; denoted in red colour) in A. the left external capsule (XYZ −27 13 −7), B. bilateral fornix/stria terminalis (XYZ −29 −23 −5), and C. left sagittal stratum (XYZ −43 −28 −13) of MA children compared to controls. The numbers in brackets represent MNI coordinates. Significant white matter regions were enhanced for improved viewing by the tbss fill function of FSL. L denote left hemisphere, and R denote right hemisphere.

Table 1

Demographic and anthropometric information of methamphetamine exposed children and controls.

	MA	Controls	Statistics
Child			
Age (years, SD)	6.71 (0.40)	6.83 (0.39)	$t = 0.86$, $p = 0.40$
Sex (*n*, male/female)	9/8	5/10	$\chi^2 = 1.24$, $p = 0.26$
Weight (kg, SD)	18.92 (2.47)	19.83 (3.11)	$t = 0.90$, $p = 0.37$
Length (cm, SD)	92.72 (7.61)	90.00 (8.45)	$t = -0.91$, $p = 0.37$
Head circumference (cm, SD)	51.79 (1.76)	51.86 (1.79)	$t = 0.10$, $p = 0.92$
Mother			
Education (years, SD)	8.81 (1.33)	9.93 (2.30)	$t = 1.65$, $p = 0.12$
Employed (*n*, no/yes)	12/4	7/8	$\chi^2 = 2.62$, p = 0.11
Marital status (*n*, %)			
Single	14(82)	7 (47)	
Married	–	6 (40)	
Living with partner	–	1 (7)	
Divorced	2(12)	–	
Widowed	–	1 (7)	

Table 2

White matter regions with altered diffusion in methamphetamine exposed children compared to controls. Affected white matter tracts mainly traversed the left hemisphere striatum and temporal lobe limbic regions.

DTI	Group effect	White matter region	Side	*XYZ*	Voxels	*p* (corrected)	Anatomical area
↓ FA	CON > MA	External capsule	Left	−27,13, −7	103	0.001	Putamen, insula, OFC
		Fornix/Stria terminalis	Left	−29, −23, −9	148	0.001	Putamen, pallidum, hippocampus, amygdala
↑ MD	MA > CON	External capsule	Left	−28,14, −5	225	0.007	Putamen, insula, OFC
		Fornix/Stria terminalis	Left	−28, −27, −6	120	0.003	Putamen, thalamus, pallidum, hippocampus
↑ RD	MA > CON	External capsule	Left	−29,13, −5	185	0.001	Putamen, insula, OFC
		Fornix/Stria terminalis	Right	26, −28, −5	85	0.013	Thalamus, hippocampus
			Left	−31, −18, −10	167	0.001	Putamen, hippocampus, amygdala
↑ AD	MA > CON	Sagittal stratum - inferior longitudinal fasciculus - inferior fronto-occipital fasciculus	Left	−43, −23, −15	57	0.006	–

Side = brain hemisphere; XYZ = MNI coordinates; Voxels = number of voxels implicated in group effect; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity; MA = methamphetamine exposed; CON = control; OFC = orbitofrontal cortex.

Table 3

Associations of fractional anisotropy with poorer cognitive test performance in children who were exposed to methamphetamine. Diffusion (as denoted by "Effect") was variably associated with motor function and aspects of executive function, probably due to compensatory alterations to brain circuitry.

Cognitive function	Test	Effect	White matter region	Side	R^2	*b*	*p*
Motor coordination	Pegboard Insert DH	↑FA	External capsule	Right	0.37	−0.42	0.038
Executive function	K-ABC-II Triangles	↓FA	External capsule	Right	0.35	0.22	0.048
	K-ABC-II Hand Movements	↑FA	Fornix/Stria terminalis	Left	0.53	−0.65	0.005
	K-ABC-II Story Completion		Sagittal stratum	Left	0.54	−0.63	0.006

Insert DH = insertion time dominant hand; FA = fractional anisotropy; K-ABC-II = Kaufman Assessment Battery for Children (version 2); side = brain hemisphere.