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Neuroimagen en adolescentes con talento matemático

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**Structural and Functional Neuroimaging in
Mathematically Gifted Adolescents**

FRANCISCO JAVIER NAVAS SÁNCHEZ

MADRID, 2015

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TABLE OF CONTENTS

List of Abbreviations.....	xi
Summary... ..	xiii
Resumen.....	xvii
• <u>Chapter 1. MOTIVATION AND OBJECTIVES</u>	1
1.1 Motivation.....	3
1.2 Objectives	6
Outline of the document.....	7
Ethics Statement.....	7
• <u>Chapter 2. INTRODUCTION</u>	9
2.1 Intelligence and Giftedness. Historical Perspective.....	11
2.2 Math-Giftedness: Enhanced Mathematical Thinking	14
2.3 Neurobiological Foundations of Math-Giftedness	16
2.3.1 Cognitive and Neurodevelopmental Precocity.....	16
2.3.2 Neuroimaging: What is the Neural Substrate of Giftedness?.....	18
2.3.2.1 Magnetic Resonance Imaging.....	18
2.3.1.2 Functional MRI	18
2.3.1.3 Diffusion Tensor Imaging	19
2.3.1.4 T1-weighted Structural MRI.....	20
2.3.3 Neuroimaging and Cognition: The Fronto-Parietal Network.....	21
2.3.4 Neuroimaging in Math-Gifted Subjects: A Gap in the Literature	22
References	26
• <u>Chapter 3. MATHEMATICALLY GIFTED ADOLESCENTS USE MORE EXTENSIVE AND MORE BILATERAL AREAS OF THE FRONTO-PARIETAL NETWORK THAN CONTROLS DURING EXECUTIVE FUNCTIONING AND FLUID REASONING TASKS</u>	31
Appendix Chapter 3	45
• <u>Chapter 4. WHITE MATTER MICROSTRUCTURE CORRELATES OF MATHEMATICAL GIFTEDNESS AND INTELLIGENT QUOTIENT</u>	51
Appendix Chapter 4	67

- **Chapter 5. CORTICAL MORPHOMETRY IN FRONTO-PARIETAL AND DEFAULT MODE NETWORKS IN MATH-GIFTED ADOLESCENTS**..... 75
 - Abstract..... 77
 - 5.1 Introduction..... 79
 - 5.2 Methods.....81
 - 5.2.1 Sample Description 81
 - 5.2.2 Magnetic Resonance Imaging Acquisition..... 82
 - 5.2.3 MRI Data Preprocessing..... 82
 - 5.2.4 Statistical Analysis 83
 - 5.3 Results 84
 - 5.3.1 Global Measurements 84
 - 5.3.2 Vertex-wise Analysis: Group Differences in Cortical Thickness 84
 - 5.3.3 Vertex-wise Analysis: Group Differences in Surface Area 86
 - 5.4 Discussion 87
 - 5.4.1 Neural Development in Math-giftedness 87
 - 5.4.2 Between-Group Differences in Cortical Morphometry: Fronto-Parietal and Default Mode Networks 88
 - 5.5 Conclusions 92
 - 5.6 References 93
 - Appendix Chapter 5 97
- **Chapter 6. GENERAL DISCUSSION AND CONCLUSIONS** 101
 - General Discussion 103
 - Conclusions 107
 - Possible Future Lines of Research 108
 - References..... 109
- PUBLICATIONS IN INTERNATIONAL JOURNALS**..... 111
 - Published Peer Reviewed Articles 111
 - Articles Submitted to International Journals..... 111

List of Abbreviations

ACC: Anterior Cingulate Cortex	IPS: Intraparietal Sulcus
ANCOVA: Analysis of Covariance	IQ: Intelligent Quotient (en castellano CI, cociente intelectual)
ANOVA: Analysis of Variance	JHU: John Hopkins University
A-P: Anterior to Posterior	mPFC: Medial Prefrontal Cortex-
BA: Brodmann Area	MNI: Montreal Neurological Institute
BET: Brain Extraction Tool	MRI: Magnetic Resonance Imaging
BOLD: Blood Oxygen-level Dependent	PET: Positron Emission Tomography
CMRO ₂ : Cerebral Metabolic Rate of O ₂	P-FIT: Parieto-Frontal Integration Theory
CSF: Cerebro-Spinal Fluid	POrb: Pars Orbitalis
CWP: Cluster-Wise Probability method	RAPM: Raven Advanced Progressive Matrices
DLPFC: Dorsolateral Prefrontal Cortex	RLPFC: Rostrolateral Prefrontal Cortex
DMN: Default Mode Network	ROI: Region Of Interest
DTI: Diffusion Tensor Imaging	SAT-M: Scholastic Assessment Test in Mathematics
EEG: Electroencephalography	SBM: Surface-Based Morphometry
EPI: Echo-Planar Imaging	SD: Standard Deviation
ESTALMAT: Estímulo del Talento Matemático	SFG: Superior Frontal Gyrus
FA: Fractional Anisotropy	SPL: Superior Parietal Lobule
FDR: False Discovery Rate	SPM: Statistical Parametric Mapping
FDT: fMRIB Diffusion Toolkit	TE: Time of Echo
FEF: Frontal Eye Fields	TOL: Towers of London
fMRI: functional Magnetic Resonance Imaging	TR: Time of Repetition
fMRIB: Oxford Center for Functional MRI of the Brain	VBM: Voxel-Based Morphometry
FNIRT: fMRIB Nonlinear Image Registration Tool	VLPFC: Ventrolateral Prefrontal Cortex
FPN: Fronto-Parietal Network	WISC-R: Wechsler Intelligence Scale for Children – Revised
FSIQ: Full-Scale IQ	
FSL: fMRIB Software Library	
FWE: Family-Wise Error	
FWHM: Full Width at Half Maximum	
GBG: ‘Geschwind, Behan, Galaburda’ model of cerebral dominance	
ICBM: International Consortium for Brain Mapping	
IPL: Inferior Parietal Lobule	

Summary

Introduction: Giftedness is a special type of intelligence that takes the form not only of higher IQ and enhanced executive functioning, but also of exceptional creativity (such as the production of novel and useful ideas) and higher motivation in specific traits. Defining giftedness only by higher IQ could lead to confusion in the identification of gifted subjects. When these abilities are applied to mathematical thinking, subjects are referred to as 'Math-Gifted'. Math-gifted subjects show higher capabilities in fluid reasoning, working memory, and mental imagery. The capacity for fluid reasoning, working memory, and mental imagery is considered to be fundamental for skilled mathematical reasoning. Neuroimaging techniques are contributing to a better understanding of the neurobiological substrate of math-giftedness. Previous studies reported that gifted individuals with exceptional mathematical ability show atypical brain functioning and atypical brain functions. Particularly, math-gifted subjects present enhanced development and greater involvement of the right hemisphere which is important for visuospatial information processing. Moreover, math-gifted individuals show heightened functional connectivity between left and right hemispheres. The enhanced interhemispheric functional connectivity together with a greater involvement of the right hemisphere may cause a special form functional bilateralism in fronto-parietal. Some neuroimaging studies reported significant associations between not only neural activations, but also white matter microstructure or cortical morphometry, and cognitive skills such as intelligence or creativity. However, to our knowledge, no studies on white matter microstructure have confirmed heightened connectivity in math-gifted subjects. In the same way, there are no studies about cortical morphometry in gifted subjects.

Objectives: The main objective of this thesis is to investigate the biological substrate of math-giftedness using three different neuroimaging modalities: (1) task-based functional MRI, (2) Diffusion Tensor Imaging and, (3) T1-weighted structural MRI. This thesis describes the brain of math-gifted adolescents not only functionally but also assessing white matter properties, structural connectivity and cortical morphometry.

The specific objectives pursued in this thesis are:

1. To investigate the neural substrate of fluid reasoning and visuospatial working memory in adolescents with mathematical giftedness as compared with age-matched controls.
2. To assess the relationship between math-giftedness and IQ with white matter microstructure in math-gifted adolescents and age-matched controls.
3. To study cortical morphometry, specifically cortical thickness and surface area, in math-gifted subjects as compared with controls group-matched in IQ and age levels.

Material and Methods: We recruited 13 adolescents (8 males and 5 females aged 12-14 years; mean IQ=130) with math-giftedness that were enrolled in the *Stimulus of Mathematical Talent Program* (ESTALMAT-“*Programa de Estimulo del Talento Matemático*”) of the Spanish Royal Academy of Mathematical, Physical and Natural Sciences in Madrid. Controls, from the same region, were group-matched by age with the math-gifted group. For the fMRI study (**chapter 3**) we recruited 14 aged-matched controls (5 females aged 12-14 years; mean IQ=90); for the DTI study (**chapter 4**) we extend the control sample to 23 adolescents (5 females aged 12-15 years; mean IQ=105); and finally, for the cortical morphometry study (**chapter 5**) we select a special sample of 17 controls that were group-matched not only in age but also in IQ score (6 females aged 11-15 years; mean IQ=123). All the enrolled subjects had to pass an IQ test and a neuroimaging study.

For the fMRI study we used two tasks related with fluid reasoning and executive functioning in a block design. The Towers of London (TOL) test is a visuospatial working memory task; with this task we tried to assess the executive functioning of the subjects. The Raven Advanced Progressive Matrices (RAPM) is a task used to assess fluid reasoning. The software used for the image processing was the Statistical Parametric Mapping (SPM v.5). For the assessment of the white-matter properties we used Diffusion Tensor Imaging (DTI). Data were processed with FSL (FMRIB Software Library v.4) to obtain fractional anisotropy maps and statistical analyses. Finally, we carried out a cortical morphometry analysis using T1-weighted structural images. The advanced Surface-based Morphometry methodologies allowed us to extract the cortical thickness and the surface area from structural T1 images. Thus, we used the software FreeSurfer to extract brain surfaces (grey/CSF and white/grey matter boundaries) and obtain cortical thickness and surface area maps, as well as to carry out the statistical vertex-wise analyses.

Results: In the fMRI study, math-gifted subjects showed a pattern of greater bilateral activation in the fronto-parietal network, as compared with controls, while performing fluid reasoning (RAPM) and executive functioning tasks (TOL). The math-gifted group presented extended activations and new regions activated when increased task difficulty whereas controls presented no differences between easy and difficult trials.

In the DTI study, math-gifted subjects presented higher FA values in large fronto-parietal and fronto-striatal association tracts. Moreover, there was a positive correlation between FA values and IQ scores in the corpus callosum.

And finally, in the cortical morphometry study, as compared with controls (group-matched in IQ), math-gifted subjects presented thinner cortex and larger surface area in key regions of fronto-parietal network and default mode network.

Discussion and Conclusions: The findings reported in this thesis highlight the special brain characteristics in terms of functionality, structural connectivity and cortical morphometry. Altogether, our results suggest that math-gifted subjects present atypical brain functioning, as well as

heightened structural connectivity and above-their-age cortical features. The enhanced connectivity between hemispheres (via corpus callosum) might be associated with the functional bilateralism in math-giftedness. In the same way, the heightened white matter microstructure between frontal and parietal regions could be related with the fronto-parietal activations, as well as, with the thinner cortex presented in these regions. These data reveals that the superior capacity in fluid reasoning and executive functioning, as well as the exceptional creativity, of math-gifted subjects could be underlie by an unique pattern of activations accompanied by grater structural connectivity and above-their-age cortical morphometry supporting the Three-Rings Model of J. Renzulli (1978).

The main conclusions of this thesis are:

1. Math-gifted group present greater bilateralism of activation in the fronto-parietal network, which is probably associated with the higher capacity of math-gifted subjects to solve complex visuospatial and analytical tasks demanding logical thinking.
2. Math-gifted group show extended pattern of activations while increasing task difficulty.
3. The functional bilateralism of the fronto-parietal network could be related with the heightened structural connectivity in fronto-parietal and frontostriatal association tracts, as well as with white matter microstructure of the corpus callosum.
5. Math-gifted adolescents show thinner cortex and larger surface area in key regions of the fronto-parietal and default mode networks in charge of executive processing and creative thinking, respectively. The combination of reduced cortical thickness and larger surface area in these regions suggests the presence of an above-their-age neural maturation in gifted individuals.

Resumen

Introducción: Un talento representa una forma especial de inteligencia que muestra un alto cociente intelectual y funcionamiento ejecutivo, una creatividad excepcional y una mayor motivación en ciertos rasgos específicos. Cuando uno de estos rasgos es el pensamiento matemático, a estos sujetos se les conoce como talentos matemáticos. Por esto, el hecho de definir a un talento únicamente por su mayor cociente intelectual podría dar lugar a confusión en la identificación de estos sujetos. Los talentos matemáticos muestran mayor capacidad de razonamiento fluido, memoria de trabajo y en imaginación mental. Estas capacidades se consideran fundamentales en el razonamiento matemático. Las técnicas de neuroimagen están contribuyendo a una mejor comprensión del sustrato neurobiológico de los talentos matemáticos. Estudios previos describieron que estos talentos muestran unas funciones cerebrales atípicas. En particular, los talentos matemáticos presentan mayor desarrollo y activación del hemisferio derecho, que es importante para el procesamiento de la información visoespacial. Los sujetos con talento matemático muestran una gran conectividad funcional entre los hemisferios izquierdo y derecho. Esta gran conectividad funcional inter-hemisférica junto con la mayor participación del hemisferio derecho podría causar una forma especial de bilateralidad funcional en la red fronto-parietal. Algunos estudios de neuroimagen describen asociaciones significativas entre las activaciones neuronales, o bien la microestructura de la sustancia blanca o bien morfometría cortical, y las habilidades cognitivas de los sujetos, tales como la inteligencia o la creatividad. Sin embargo, hasta donde hoy sabemos, no hay estudios sobre el estado de la sustancia blanca que confirmen la mayor conectividad estructural entre diferentes regiones cerebrales en talentos matemáticos. Así mismo, a día de hoy no existen estudios sobre morfometría cortical en talentos matemáticos.

Objetivos: El objetivo principal de esta tesis es investigar el sustrato biológico del talento matemático utilizando tres modalidades diferentes de imagen por resonancia magnética (MRI): (1) la MRI funcional basada en tarea; (2) la imagen por tensor de difusión o DTI; y (3) la imagen estructural ponderada en T1. Con esta tesis se va a describir el cerebro de un talento matemático no sólo en cuanto a su función, también en cuanto a las características de la sustancia blanca y a su morfometría cortical. Los objetivos específicos propuestos en esta tesis son los siguientes:

1. Investigar el sustrato neural del razonamiento fluido y de las funciones ejecutivas, así como la memoria de trabajo visoespacial, en adolescentes con talento matemático y en controles de la misma edad.

2. Evaluar la relación entre el talento matemático así como del cociente intelectual, y la microestructura de la sustancia blanca en el cerebro de adolescentes con talento matemático y controles de la misma edad.

3. Estudiar la morfometría cortical, específicamente el grosor cortical y el área de la superficie, en adolescentes con talento matemático y controles de la misma edad y nivel intelectual.

Material y métodos: Se reclutaron 13 adolescentes con talentos matemático (5 mujeres, con edades comprendidas entre 12-14 años y un IQ = 130 de media), que estaban inscritos en el programa estatal de Estímulo del Talento Matemático (ESTALMAT) de la Real Academia de Matemáticas, Física y Ciencias Naturales de Madrid. Los controles, de la misma región, se reclutaron de acuerdo a la edad y el nivel socio-económico, para poder emparejar un grupo con otro. Para el estudio de resonancia magnética funcional (capítulo 3) reclutamos 14 controles de la misma edad (5 mujeres entre 12-14 años; IQ media = 90); para el estudio DTI (capítulo 4) ampliamos la muestra de control a 23 adolescentes (5 mujeres entre 12-15 años; IQ media = 105); y, finalmente, para el estudio de morfometría cortical (capítulo 5) seleccionamos una muestra especial de 17 controles que fueron pareados por grupos no sólo en edad sino también en la puntuación de cociente intelectual (6 mujeres de entre 11-15 años; IQ = 123 media). Todos los sujetos inscritos tuvieron que pasar un test de inteligencia y un estudio de neuroimagen en la misma sesión.

Para el estudio fMRI (*capítulo 3*) hemos utilizado dos tareas relacionadas con el razonamiento fluido y el funcionamiento ejecutivo mediante un paradigma con un diseño de bloques. Las torres de la prueba de Londres (TOL) es una tarea de memoria de trabajo visoespacial, queremos evaluar el funcionamiento ejecutivo de los sujetos. La escala avanzada de las Matrices Progresivas de Raven (RAPM) es una tarea clásica utilizada para evaluar el razonamiento fluido. El software que se ha utilizado para el procesamiento de imágenes funcionales es el *Statistical Parametric Mapping* (SPM v.5). Para el estudio de las propiedades de la sustancia blanca y conectividad estructural hemos utilizado la imagen por tensor de difusión (DTI). En este estudio (*capítulo 4*) se utilizó el software FSL (FMRIB Software Library v.4.1) con el fin de obtener los mapas de fracción de anisotropía, procesar las imágenes y realizar los análisis estadísticos. Y por último, para el estudio de morfometría cortical (*capítulo 5*) hemos utilizado imágenes estructurales ponderadas-T1. Las avanzadas metodologías morfometría basada en superficie nos permiten extraer el espesor cortical y el área superficial de la imagen T1 estructural. En este estudio se utilizó el software FreeSurfer v.5.3 para extraer las superficies cerebrales (límite entre gris/CSF y límite entre materia blanca y gris), y obtener a partir de ellas los mapas de espesor y superficie cortical, así como llevar a cabo los análisis estadísticos basados en vértices.

Resultados: En primer lugar, en el estudio de resonancia magnética funcional, los adolescentes con talento matemático mostraron un patrón de activaciones bilaterales en la red fronto-parietal mayor, en comparación con los controles. Este patrón está relacionado con la realización de tareas de razonamiento fluido (en este caso, RAPM) y de funcionamiento ejecutivo (en este caso TOL). El grupo de talentos matemáticos presentó una extensión mayor de las activaciones y nuevas regiones cuando se incrementó el nivel de dificultad de la tarea, mientras que los controles no lo mostraron.

En segundo lugar, en el estudio DTI, los adolescentes con talento matemático presentan valores más altos de FA en grandes tractos de asociación fronto-parietal y fronto-estriatal. Por otra parte, existe una correlación positiva entre los valores de FA y puntuaciones de CI en el cuerpo caloso. Y, por último, en el estudio de morfometría cortical, en comparación con los controles (grupo pareado en el cociente intelectual), los adolescentes con talento matemático presentan una corteza cerebral más delgada además de una mayor superficie en regiones clave de la red fronto-parietal y la red de modo por defecto (DMN).

Discusión y conclusiones: Los hallazgos mostrados en esta tesis ponen de manifiesto las características especiales del cerebro de los talentos matemáticos en términos de funcionalidad, conectividad estructural y morfometría cortical. En conjunto, nuestros resultados sugieren que los talentos matemáticos presentan un funcionamiento atípico del cerebro, así como una mayor conectividad estructural y unas características corticales que son las encontradas típicamente en sujetos mayores a su edad. La mayor conectividad inter-hemisférica (a través del cuerpo caloso) podría estar asociada con la atípica bilateralidad funcional mostrada por los talentos. De la misma manera, la mayor microestructura de la materia blanca entre las regiones frontal y parietal podría estar relacionada con las activaciones fronto-parietales, así como, con la corteza más delgada presentada en estas regiones. Todos estos datos revelan que las altas capacidades en razonamiento de fluido y funcionamiento ejecutivo, así como la creatividad excepcional, de los talentos podrían estar relacionadas con un patrón de activaciones único acompañado de la mayor conectividad estructural y con una morfometría cortical adelantada a su edad, apoyando el modelo de los Tres Anillos de J. Renzulli (1978).

Las principales conclusiones de esta tesis son:

1. Los adolescentes con talento matemático presentan mayor bilateralidad funcional de la red fronto-parietal. Esta funcionalidad atípica probablemente esté asociada con una mayor capacidad de los adolescentes con talento matemático para la resolución de problemas complejos y novedosos.
2. Los adolescentes con talento matemático muestran mayor extensión de las activaciones al tiempo que aumenta la dificultad de la tarea.
3. La bilateralidad funcional de la red fronto-parietal podría estar relacionada con la mayor conectividad estructural interhemisférica del cuerpo caloso, así como con la mayor conectividad estructural en tractos de asociación fronto-parietal y fronto-estriales.
5. Los adolescentes con talento matemático muestran una corteza cerebral delgada y mayor superficie en regiones clave de las redes de modo fronto-parietal y DMN a cargo del procesamiento ejecutivo y el pensamiento creativo, respectivamente. La combinación de la reducción de espesor cortical y el área de superficie mayor en estas regiones sugiere la presencia de características de maduración cortical por encima de su edad.

Chapter1. Motivation and Objectives

1.1 Motivation

There is an increasing interest in the neural basis of intelligence, as well as in the comprehension of the underlying processes of intelligence and giftedness. Some authors suggested that intelligence is a general ability that constitutes the main core of giftedness. Thus, giftedness behavior could be measured and expressed by a single number, such as the IQ score (specifically is consider 2 standard deviations above the average). On the other hand, some other authors suggested that intelligence encompasses a range of aptitudes, skills, and talents and hence, the merely use of the IQ score to define a different behavior could oversimplify the question. In these days, the definition of both ‘intelligence’ and ‘giftedness’, are still under debate. However, in the academic domain ‘giftedness’ is defined as a psychological construct (based on the *Renzulli’s Model*), which has to combine (1) higher IQ levels (superior general intelligence), (2) exceptional creativity and (3) high specific-task commitment (or intrinsic motivation) in certain areas, such as mathematics (Renzulli, 1978). Mathematical giftedness is associated with mathematical thinking, which is in turn related with comprehension, as well as with organizing and systematizing ideas to discover the rules that govern processes. In mathematical thinking is crucial the ability to perceive complex relations, abstraction and new concepts formation. It is not only associated with numbers, equations or algebra, but also with geometry, visuospatial processing and logical reasoning.

Regarding the cognitive properties of mathematical thinking, visuospatial working memory and fluid reasoning have been postulated as the core of math-giftedness. Fluid reasoning is the ability to perceive complex relations using in working memory, concept formation, reasoning, and abstraction. Thus, it participates in several mental processes such us the formation of constructs, logical reasoning and abstract concepts. Working memory is the ability to hold and manipulate that information during novel problem solving (Gray, et al., 2003; Lee, et al., 2006).

Previous neuroimaging studies using fMRI and PET techniques showed that both processes, fluid reasoning and visuospatial working memory, are related to the fronto-parietal network (Fincham, et al., 2002; Lee, et al., 2006; Van den Heuvel, et al., 2003). This also suggest that these cognitive processes may share the same neural substrate (Colom, et al., 2003; Colom, et al., 2007; Lee, et al., 2006; Prabhakaran, et al., 1997). The fronto-parietal network coordinates the activation processes between different brain regions and other networks integrating different types of information (Christoff, et al.,

2001; Goldman-Rakic, 1995; Gray, et al., 2003). This information is created, maintained, processed and manipulated mainly in the parietal lobes (Harris, et al., 2000.; Just, et al., 2001; O'Boyle, et al., 2005). Although the fronto-parietal network is one of the most important brain networks involved in math-giftedness, there are some others such as the dorsal attentional network which is also important in fluid reasoning and working memory processes, and hence related with mathematical giftedness.

Neurobiologically, math-gifted adolescents showed atypical neural characteristics in the fronto-parietal network as compared with math-average subjects (Alexander, et al., 1996; O'Boyle, 2008; O'Boyle, et al., 2005; Prescott, et al., 2010a; Singh and O'Boyle, 2004; Terao, et al., 2004). Some authors support that math-gifted subjects present functional bilateralism in the fronto-parietal regions related with an increased functional activation and development of the right hemisphere (Benbow, 1986; Benbow and Lubinski, 1993; O'Boyle, et al., 1991; O'Boyle, et al., 2005). The higher contribution of the right hemisphere in certain tasks is associated with a greater specialization of this hemisphere in information processing capabilities visuospatial (Geschwind and Galaburda, 1984; Geschwind and Galaburda, 1987; O'Boyle, et al., 1991; O'Boyle, et al., 1995; O'Boyle, et al., 2005). These two characteristics would imply greater connectivity and greater exchange of information between the left and right hemispheres (Alexander, et al., 1996; Singh and O'Boyle, 2004). Singh and M. O'Boyle (2004) suggested that greater coordination of resources between cortical hemispheres is a unique functional characteristic of math-giftedness. Furthermore, the activation of both hemispheres and their interaction seems to be essential for complex mathematical thinking (Dehaene, et al., 1999).

Although over the last 10 years different neuroimaging studies aimed to describe the functional properties of math-gifted subjects, none of those studies were focused on assessing other brain features such as white-matter microstructure or cortical morphometry. The study of these brain features is needed to complete a global picture of the brain characteristics of math-gifted subjects.

The assessment of white-matter microstructure with Diffusion Tensor Imaging (DTI) techniques becomes important to assess the structural connectivity between frontal and parietal regions as well as between the left and right hemispheres. DTI techniques evaluate the quality of the axons that interconnect different regions in the brain. Neural processes such as myelination are crucial for some cognitive functions. Previous studies

described the relationship between intelligence scores, creativity or working memory with the white-matter microstructure (Nagy, et al., 2004; Schmithorst and Holland, 2007; Schmithorst, et al., 2005; Takeuchi, et al., 2010; Yu, et al., 2008).

Furthermore, the study of cortical properties (thickness, surface area or volume) could provide new insight on brain features of math-gifted subjects. Although the relationship between cortical structure and function still remains a challenge at these days, previous studies reported relationships between cortical morphometry and some cognitive scores, such as intelligence scores, working memory and creativity (Fjell et al. 2006; Shaw et al. 2006; Narr et al. 2007; Luders et al. 2009; Jung et al. 2010; Tamnes et al. 2010b; Karama et al. 2011; Burzynska et al. 2012; Colom et al. 2013; Skranes et al. 2013; Schnack et al. 2014; Fjell et al. 2015).

This Thesis intend to complete the global picture of the neurobiological features of a math-gifted's brain. In order to do so, we made use of advanced neuroimaging techniques to carry out new studies about brain functional and structural properties.

Moreover, most of previous neuroimaging works defined giftedness as high-level IQ, disregarding the exceptional creativity. This thesis, in agreement with the *Three-Rings Model* proposed by Renzulli (1978), tries to address the problem with a wider scope. The sample recruited for this work pertained to ESTALMAT, the national program to stimulate the mathematical giftedness in children and adolescents (<http://www.estalmat.org/>). The tests used by the ESTALMAT program assure that the selected sample meets the requirements of the neuropsychological concept of giftedness (including creativity and task-commitment assessments) (Kießwetter, 1985).

Based on the above mentioned prior studies of math-giftedness and previous data from normal subjects, we hypothesized that the cognitive behavior of math-giftedness would entail not only special functional characteristics, but also greater structural connectivity and cortical features non-dependent of the IQ. More specifically, we could predict that these differences would affect regions of the fronto-parietal executive network and other key regions related with information processing.

1.2 Objectives

The main objective of this Thesis is to investigate the neural substrate of math-giftedness using three different neuroimaging techniques: (1) task-based functional MRI, (2) Diffusion Tensor Imaging and, (3) T1-weighted structural MRI. Thus, the brain of a math-gifted adolescent will be described not only functionally but also assessing white matter properties, structural connectivity and cortical morphometry.

The specific objectives of this thesis were:

1. To investigate the neural substrates of fluid reasoning and visuospatial working memory in adolescents with mathematical giftedness as compared with age-matched controls. We used task-related fMRI techniques with the Raven Advanced Progressive Matrices (RAPM) and the Tower of London (TOL) tests.
2. To assess the relationship between math-giftedness and IQ with white matter microstructure in math-gifted adolescents and age-matched controls.
3. To study the cortical morphometry, specifically the cortical thickness and the surface area, in math-gifted subjects as compared with controls group-matched in IQ and age levels.

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Outline of the document

The present document is organized into six chapters. **Chapter 2** presents a general introduction to math-giftedness and describes the ‘state of the art’ in the field of neuroimaging focused on math-giftedness. **Chapter 3** presents a task-related fMRI study in 13 math-gifted subjects and 13 age-matched controls using the ‘Towers of London test’ as executive functioning assessment, and the ‘Raven Advanced Progressive Matrices’ as fluid reasoning assessment. **Chapter 4** presents a DTI study intending correlates math-giftedness and IQ with white matter microstructure. We used the same 13 math-gifted adolescents and 23 controls. We used both voxel-based and ROI analyses. **Chapter 5** presents a cortical morphometry study using surface-based methodologies that allows segregating the cortical thickness and surface area from the cortical volume. The same 13 math-gifted subjects were compared with 17 controls group-matched in IQ and Age. **Chapter 6** presents the general conclusions of the thesis and some ideas about possible future work.

Ethics Statement

All the studies that conducted within this PhD Thesis were approved by the Ethics and Clinical Research Boards of the Gregorio Marañón General Hospital. Written informed consent was obtained from the subjects and parents before the study began.

Chapter 2. Introduction

2.1 Intelligence and Giftedness. Historical Perspective

"I know that I am intelligent, because I know that I know nothing". Socrates

Throughout history, philosophers and psychologists have been interested in the neural basis of individual differences in cognitive functions. Intelligence is the cognitive function that most contributes to variability in human behavior, and then, one of the most widely studied. For centuries, philosophers have tried to pinpoint the true measure of intelligence. Since 2200 b.C. Chinese people have developed different systems of competitive examinations to select outstanding individuals for government positions (DuBois, 1970). However, nowadays even the definition of intelligence is still under debate. Recently, the neuroscientists have entered the debate, searching for answers about intelligence from a biological perspective: What makes some brains brighter than others?

Since Charles Spearman in 1904 proposed the first theory of intelligence, many authors tried to define this construct in many ways. Spearman advocated for a general intelligence factor called "g," which remains controversial to this day. He proposed that if people tend to do well on some sections of an IQ test, they tend to do well on all of them. In disagreement with that conception of intelligence, Robert Sternberg in his *Triarchic Theory of Intelligence* (1985) argued that previous definitions of intelligence were too narrow because they were solely based on intelligences that can be assessed in IQ test. Instead, Sternberg proposed that intelligence could be broken down into three fields: analytic, creative, and practical intelligence. Finally, Howard Gardner with his *Theory of Multiple Intelligences* (1988) proposed 8 types of intelligence claiming that there was no correlation between them. Although the construct of 'Intelligence' has been changed (in order to include factors that constrain the definition), it is noteworthy to remember that 'Intelligence' derives from the Latin verb *Intelligere*, which means to comprehend or to perceive. People who show different forms to perceive the reality have a greater abstraction capabilities, which is very useful in order to solve novel problems.

"The true sign of intelligence is not knowledge but imagination". Albert Einstein

In parallel to the construct 'Intelligence', the challenge is to define 'Giftedness'. The terms 'Giftedness' and 'Intelligence' are fluid concepts and may look different in different contexts and cultures. At these days there is no any universally accepted definition of 'Giftedness'. The conceptual foundation of giftedness was initially based on

measurement of intelligence. In the twenties (1920), Lewis Terman defined giftedness as the top 1% level in general intellectual ability, as measured by an Intelligence Scale. Gifted children tend to score high on tests of general intelligence (Mrazik and Dombrowski, 2010). However, a single IQ test does not adequately assess the wide variety of abilities that gifted individuals may display in some specific fields. Afterwards, some theories involving more multifaceted approaches to giftedness were proposed to expand the concept of giftedness (Aiken, 1973; Kalbfleisch, 2004; Kießwetter, 1985; Renzulli, 1978; Renzulli, 1998; Sternberg, 2010; Sternberg and Davidson, 2005). Among these theoretical conceptions of giftedness, one of the most significant model is the ‘Three-Rings model’ proposed by Joseph Renzulli in 1978. Until this year, there was no a unified conceptual definition of ‘Giftedness’. In his famous article “*What makes Giftedness?*” Renzulli (1978) described three traits or factors involved in gifted behavior (1) above average intelligence or general abilities, (2) high task commitment or intrinsic motivation and (3) high creative thought (**Figure 2. 1.**). Renzulli, with this article builds the basis of the broad conception of giftedness. It is remarkable that no single cluster “makes giftedness”. It is necessary the interaction among the three clusters for creative/productive accomplishment. Accordingly, a gifted subject is an individual who presents, at least, a general intelligence above the average of the population, with an intrinsic motivation focused on a general or specific area and, a greater creative thought. Since the *Three-Rings model* was formulated, all the operational definitions of ‘Giftedness’ vary but present these three main clusters as the basis.

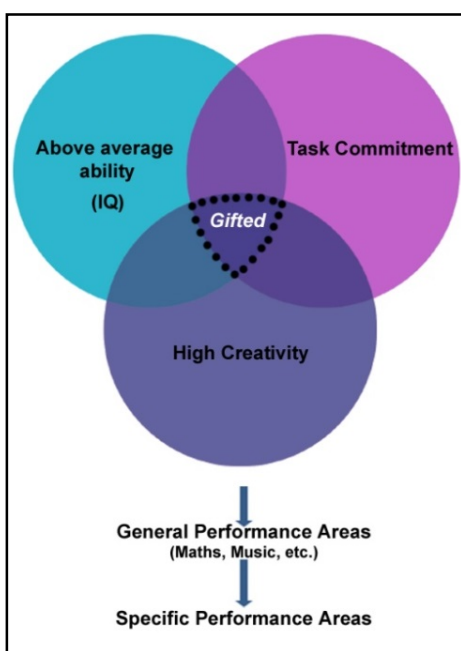


Figure 2. 2. *The Three-Rings model of Renzulli (1978). Giftedness emerges from the interaction between the three traits or factors: (1) above average abilities, (2) task commitment and (3) creativity.*

In the same way, Gagné proposed in 1985 the *Differentiated Model of Giftedness and Talent*. In his model, the term *giftedness* designates the possession and use of untrained and spontaneously expressed natural abilities (called aptitudes or gifts) in at least one ability domain, to a degree that places the subject among the top 10% of his or her age peers. His model presents four aptitude domains: intellectual, creative, socioaffective and sensorimotor (Gagné, 1985). More recently, Layne Kalbfleisch (2004) also extended the Renzulli's model: '*From developmental perspective, a child is cognitively "gifted" when their aptitude/IQ measures approximately two standard deviations above the norm (IQ>130) on psychometric measures of intelligence and when they display certain behaviors or traits such as creativity, exceptional memory, rapid processing speed, high motivation, an affinity for learning, and optimal cognitive performance in one or more domains*' (Kalbfleisch, 2004). A few years ago, John G. Geake reviewed different works that characterized the brain of gifted people, and combining the neurobiological and related cognitive characteristics of gifted people proposed the *Neuropsychological Model of High Creative Intelligence* (Geake and Dodson, 2005; Geake and Hansen, 2005). This model of creative intelligence features fluid analogizing, analogies with several plausible but no necessary correct solutions (Hofstadter, 2001; Hofstadter, 1995), as the vehicle by which dynamic information processing occurs in the brain. In this context, 'creativity' domain determines the intuitive part of giftedness, while 'Giftedness' *per se* needs an effective interplay of intuition and analytical thinking (measured by IQ or 'g').

The problem in the uses of the construct 'Giftedness' goes along the changes that the definition of 'Intelligence' suffered. Although 'giftedness' in academic and creative domains has been defined (Heller, et al., 2000; Kießwetter, 1985; Renzulli, 1978; Sternberg and Davidson, 2005), in neuroscientific studies is operationalized as either achieving high levels of general intelligence on standardized IQ test or demonstrating precocious levels of performance in educational settings. Summarizing, all of the definitions of 'giftedness' have common points such as higher intellectual abilities scores and higher creativity levels in certain traits. Although authors such as Renzulli, Kalbfleisch or Geake had proposed an overlap between intelligence and creativity, nowadays there is no commonly accepted definition of giftedness. Despite the confusion about how to define 'giftedness', the mere use of the individual IQ (or an isolated intelligence score based on Spearman's model) as a predictor of giftedness seems to be

an error. For this reason, it is crucial in every study to describe the operational definition of those concepts.

2.2 Math-Giftedness: Enhanced Mathematical Thinking

Taking the *Three-Rings model* of Renzulli as an operational conception of giftedness, a gifted subject must present high intelligence scores accompanied with high creative thought and an intrinsic motivation for a specific area (Renzulli, 1978). Mathematically gifted people share a performance area: mathematics.

Mathematical thinking is not the same as ‘doing math’. Mathematical thinking is associated with comprehension, understanding, and using patterns, as well as with organizing and systematizing ideas to discover the rules that govern processes. The ability to perceive complex relations, abstraction and new concepts formation is crucial in mathematical thinking. It is not only associated with numbers, equations or algebra, but with geometry, visuospatial thinking and logical reasoning.

Fluid reasoning, working memory, and mental imagery are thought to be essential for mathematical thinking (Gray, et al., 2003; Lee, et al., 2006). Fluid reasoning is the ability to perceive complex relations and engage in working memory, concept formation, reasoning, and abstraction. Working memory makes it possible to retain and manipulate information from intermediate steps while solving a problem (Baddeley, 2003). Mental imagery is the ability to visualize mental images that are structurally similar to perceptions during reasoning, in order to find new information not explicitly given in the premises; this ability makes it easier to clarify and understand data and the relationships between them. These relationships may be tangible (e.g., graphs, maps, or three-dimensional models) or mental (e.g., mental images that can be used during reasoning to find new information not explicitly given in the problem) (Knauff, et al., 2002).

Math-gifted subjects show higher capabilities of fluid reasoning, working memory, and mental imagery (Lee et al., 2006; O'Boyle et al., 2005). A math-gifted individual is someone who show, since childhood, good logical-mathematical abilities (capacity of abstraction), and visuospatial skills (ability to create and manipulate mental images) superior to the rest. Math-gifted subjects perform better in novel problem solving by using innovative selection criteria and are able to perceive complex relations and form concepts faster than non-gifted subjects (Kalbfleisch, 2004; O'Boyle, et al., 2005). In addition, they

store and manipulate outcomes more efficiently and creatively. The creative aspects of intelligence are accompanied by enhanced cognitive processes such as fluid reasoning and working memory (Geake and Hansen, 2005). Creative thinking includes the capabilities of flexible information processing, reversing the train of thoughts, using original methods for problem solving, considering alternative solutions, etc. (Banfield, 2005; Sak, 2004). Mathematically creative thinking is intuitive or unconscious, rather than strictly logical, formal, and conscious, and that is what really makes math-giftedness a special behavior. The characteristics of math-giftedness seem to be innate and are related to the intuitive (Mrazik and Dombrowski, 2010)

However, the conceptual problem of ‘what is giftedness’ is still there, and most of the articles about math-giftedness focused on the presence of an IQ two standard deviations higher than the average population, or on the precocious SAT-Math (Scholastic Aptitude Test in Mathematics) scores. This approach restricts, or limits, to some extent the concept of gifted and all the capabilities that can define a gifted individual. Of course it is well-known that gifted people present a precocious cognitive development, but the problem raises with the tests used to construct ‘Giftedness’.

2.3 Neurobiological Foundations of Math-Giftedness

2.3.1 Cognitive and Neurodevelopmental Precocity

One of the main features of gifted children is the precocity showed not only in intellectual performance but also in certain traits such as focused attention, evaluative selection. As Kalbfleisch proposed, is important to remark that we have to talk about giftedness from a developmental perspective (Kalbfleisch, 2004). Based on this idea, Geake, Gross and other authors proposed the ‘Above-age Testing’ as a good approach to accurately assess the academic and intellectual abilities of gifted children whose scores are higher on age-normed standardized tests (Gross, 2004). The hypothesis behind above-age testing is that gifted children are more similar (at least cognitively) to older children than to their same-age peers. This idea is not baseless: in 1996, Alexander and O’Boyle compared the alpha signal obtained from the electroencephalographic records (under resting-state condition) of 30 math-gifted adolescents (13 years) with a group composed by 30 average-ability age-matched peers (13 years) and other group composed by 30 college students (20 years). They found no differences in EEG signal at the frontal and occipital lobe locations between gifted adolescents and college group, while these two groups presented significantly less alpha power values than the average-ability group. This result suggests that gifted subjects present a brain activity similar to the level typically found in adults. In other words, the frontal lobes of the young gifted subjects seemed to be operating with a similar maturity of students about seven years older, already at university level (Alexander, et al., 1996). Thus, accompanying the intellectual precocity might occurs a precocious brain development. Different studies focused on the neurobiology of cerebral dominance could support this hypothesis (Benbow, 1986; Geschwind and Galaburda, 1984; Geschwind and Galaburda, 1987).

In 1984, Normand Geschwind and Albert Galaburda investigated patterns of asymmetry in brain morphology and physiology and their relationship with intelligence (Geschwind and Galaburda, 1984). Their findings had direct implications for understanding giftedness. The authors argued that mild abnormalities of neural migration in early stages of the development are not only involved in disorders of the nervous system but also could manifest themselves into superior abilities. The model of cerebral dominance reported by Geschwind and Galaburda (Geschwind and Galaburda, 1984; Geschwind and Galaburda, 1987) argued that high levels of testosterone in utero may

inhibit some aspects of the brain development (typically aspects of left-hemisphere functioning) while enhancing other areas (typically right brain development). In these cases, subjects presenting greater right-hemisphere development would present signals of precocity, although they are also more likely to show with disabilities of verbal-language development and health concerns (Geschwind and Galaburda, 1987). Supporting this hypothesis, Geschwind and colleagues suggested a link between a higher incidence of autoimmune disorders, asthma, allergies, and myopia among individuals with left or mixed handedness (Geschwind and Behan, 1982; Geschwind and Galaburda, 1987). Other studies (Benbow, 1986; Dehaene, et al., 1999) investigated extremely mathematically precocious youth and also found a much higher prevalence of these disorders in gifted populations. Camilla Benbow in 1986 also proposed that greater development of the right cerebral hemisphere may be associated with extreme intellectual giftedness due to the influence of testosterone. More recently, Fingelkurts & Fingelkurts (2002) extended the argument of the existence of a connection between high intelligence and high testosterone levels in the prenatal fetus in a review of different studies focused on monozygotic male twins (Fingelkurts and Fingelkurts, 2002).

Finally, in the last decade, the neuroimaging studies of Michael W. O'Boyle and colleagues appeared to support the Geschwind 's hypothesis of atypical brain development and its explanation of giftedness, citing that exposure to testosterone during the second trimester accounted for the much higher ratio of males to females in mathematically gifted youths (O'Boyle, et al., 1995; O'Boyle, et al., 2005). Based on some of these studies focused on the biological characteristics of math-giftedness, it seems that neuroimaging may be an appropriate technique to study brain features in math-gifted subjects.

At these days, neuroscience is contributing to a better understanding of the biological foundations of mathematically gifted brains. In neuroimaging, development of new and advances techniques over the last 10 years made it possible to study the macrostructure of the brain in vivo. In this thesis we make use of different neuroimaging modalities focusing on math-giftedness. The next section briefly presents some of those techniques.

2.3.2 Neuroimaging: What is the Neural Substrate of Giftedness?

2.3.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a group of medical imaging techniques that appeared recently and have experienced a rapid progress. It provides images with good spatial resolution and excellent contrast of soft tissues. It is based on a physical phenomenon discovered called nuclear magnetic resonance. This is a phenomenon whereby certain atomic nuclei are able to absorb and emit electromagnetic energy in a very precise frequency (resonance) when subjected to an intense magnetic field. The MRI scanner creates such a strong magnetic field that aligns the spins of some atomic nuclei. Then, the machine emits a short pulse of radio frequency energy. Protons absorb this energy to the resonant frequency, realigning at an oblique angle to the magnetic field. After the magnetic pulse, an antenna receives the energy released by the nuclei of atoms excited when they return to balance. The relaxation time of the nuclei is different depending on their environment (Gibby, 2005). Although there are several elements of biological interest whose nuclei exhibit the phenomenon of magnetic resonance (hydrogen, phosphorus, sodium, etc.), imaging systems for clinical use only work with hydrogen nuclei yet. The images are obtained using a magnetic resonance scanner, which generates digital images in which each pixel (imaging unit) represents a value related to the relaxation time of the tissue or other physical-chemical parameters thereof. One of the biggest advantages of MRI is that it is a non-invasive and safe technique. Besides structural imaging, MRI has many varieties, such as functional MRI which explores brain activation patterns using BOLD contrast, or diffusion tensor imaging (DTI) which allows us to assess some white matter properties (myelination, integrity, etc.).

2.3.1.2 Functional MRI

Functional MRI (fMRI) is a non-invasive tool for studying brain function. Functional MRI relies on detecting blood changes in relation to brain activity either in resting-state or while performing tasks. It is being used to address a wide variety of research questions, as for instance cognitive functioning, memory, attention, language, or pain. The energy required by the brain is usually expressed in terms of oxygen consumption (CMRO₂). The CMRO₂ is related to neural activity, which is four times higher in the gray matter in the white matter. The supply of oxygen and glucose is driven by cerebral blood flow. When

neurons are activated, there is a rapid local increase of oxygen consumption and demand for oxygenated blood. After about four or five seconds, the local flow increases, and the oxygenated hemoglobin exceeds the regional oxygen uptake. Thus, there is a hyperperfusion of the local tissue (more oxygen is provided than needed). Indeed, the blood with and without oxygen have different magnetic susceptibility, so signal intensity changes on the images can be detected. The oxygenated hemoglobin is diamagnetic (that is, having little effect on the regional magnetic field) while deoxygenated hemoglobin is paramagnetic (i.e., it disturbs the regional magnetic field). In this way, a relative increase in oxygenated hemoglobin produces a magnetic field variation in the region of the neuronal activation, producing a contrast in magnetic resonance signal of the image, called 'Blood-Oxygen-Level Dependent' (BOLD). This BOLD signal allows us to identify the brain regions active during cognitive processes under study (Ogawa, et al., 1990). A task-related fMRI study consists in several phases: Firstly, the design of the specific paradigm based on a particular cognitive function. This paradigm presents the stimuli in events or blocks of activation and rest.. During the stimuli presentation, synchronized images are acquired and finally, the statistical analysis of the images is carried out with specific algorithms (spatial normalization to a standard brain, statistical analysis and anatomical localization of brain activations). The result is an image with the effect size between activation and resting blocks, presented as a statistical parameter map (**Figure 2. 2**).

2.3.1.3 Diffusion Tensor Imaging

The diffusion process is the result of random translational movements (or Brownian motion) of the particles that make up matter, driven by the thermal energy of the particles. This kinetic property of matter tends to equalize the concentrations of a substance in a given volume. MRI can measure the diffusion of water, from the magnetic resonance signal measured for different directions after applying a bipolar magnetic field gradient. The diffusivity of water molecules is affected by physical barriers such as cell membranes, organelles and macromolecules (Cooper, et al., 1974). Diffusion tensor imaging, or DTI is an imaging modality that measures the directionality of water diffusion (anisotropy). This anisotropy estimation method was proposed in 1994 by Basser and colleagues (Basser, 1994). For the cerebrospinal fluid (CSF), the water moves freely producing an isotropic diffusion, that is, identical in any direction. By contrast, white

matter comprising dense packages of axonal fibers, so that an anisotropic diffusion will occur parallel to the fibers. Thus, for each voxel of the image, in a time interval, the average movement of water molecules described a sphere in the case of isotropic diffusion, or an ellipsoid in the case of an anisotropic diffusion (**Figure 2. 2**). In summary, diffusion tensor imaging (DTI) provides a framework for analysis and quantification of the diffusion properties of white matter. Specifically, fractional anisotropy (FA) makes it possible to assess myelin and axonal microstructure in white matter (Basser, 1997; Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996). Increased FA may depend on increased fiber density, increased myelination of fiber tracts, higher directionally coherent organization of fibers within voxels (Beaulieu, 2002), or increased axonal diameter (Mori and Zhang, 2006).

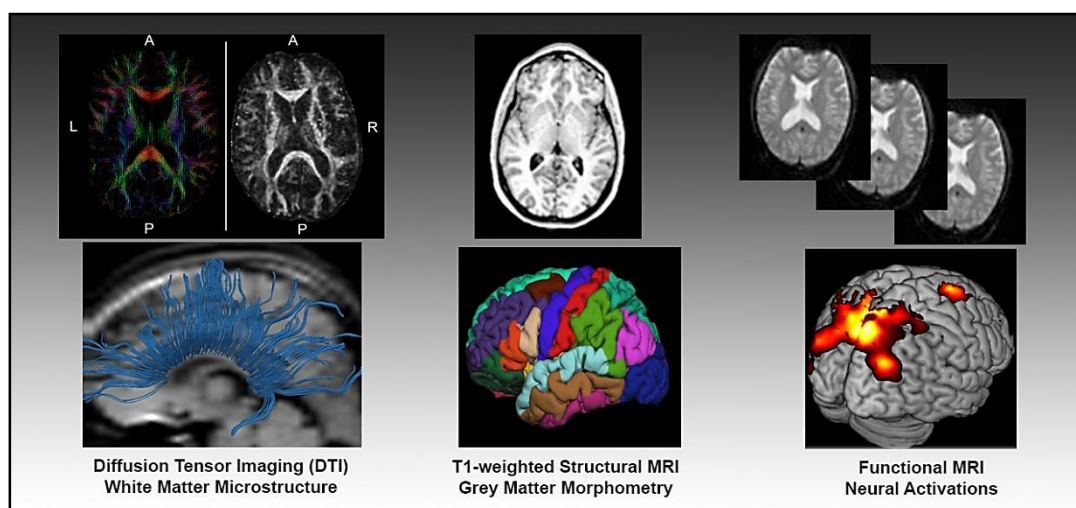


Figure 2. 3. Three MRI modalities commonly used in brain studies: Diffusion Tensor Imaging to assess the white matter microstructure (on the left); the T1-weighted Structural MRI to study cortical morphometry (on the centre); and functional MRI to study neural activations while subjects performing certain tasks (on the right).

2.3.1.4 T1-weighted Structural MRI

Conventional, or T1-weighted structural, MRI provides information on the location, shape and size of the brain tissues. This technique is based on differential composition of different tissues. The standard structural imaging study comprises two types of sequences: T1-weighted and T2-weighted. In this thesis we mostly use T1-weighted sequences, which provide greater detail of the tissues, while in T2 weighted enables better visualization of fluids (**Figure 2. 2**).

2.3.3 Neuroimaging and Cognition: The Fronto-Parietal Network

Since Jung and Haier in 2007 published the *Parieto-Frontal Integration Theory*, it is well accepted that the fronto-parietal network is related with different processes associated with ‘intelligence’. In their work, Jung and Haier reviewed different neuroimaging studies (DTI, PET, fMRI, VBM, etc.) focused on fluid reasoning, IQ, working memory, etc. They concluded that the neural differences between subjects in regions that are part of the fronto-parietal (executive and attentional) network underlay the variability in intelligence within a population.

Previous results from fMRI and PET studies showed how cognitive functions such as fluid reasoning or working memory are associated with activation of key regions of the fronto-parietal network, specifically the dorsolateral prefrontal cortex (DLPFC) and the superior parietal lobule (SPL) and intraparietal cortices (Fincham, et al., 2002; Lee, et al., 2006; Newman, et al., 2003). These fronto-parietal regions have been related to visuospatial and/or verbal working memory subsystems such as executive functioning, mental imagery (Harris et al., 2000; Just et al., 2001; O'Boyle et al., 2005), and control of spatial attentional shifts (Coull and Frith, 1998). Importantly, increasing task-related working memory load is associated with increased task-related brain activation in the DLPFC (Carpenter, et al., 1990) and superior parietal lobules (Klingberg, et al., 1997; Perfetti, et al., 2009).

As neural activations, the white matter properties can also be related with different cognitive functions such as intelligence and creativity. For example, previous studies showed a relationship between the FA and intelligence (Schmithorst and Holland, 2007; Schmithorst et al., 2005; Yu et al., 2008), arithmetic and mathematical calculation scores (Tsang et al., 2009; van Eimeren et al., 2010), working memory scores (Nagy et al., 2004), and visuospatial processing (Klingberg, 2006; Mabbott et al., 2006; Wolbers et al., 2006). Remarkably, all of these studies showed a correlation between cognitive functions and FA in white matter fronto-parietal areas (among others). These correlations were thought to reflect a positive relationship between white matter organization and higher intelligence, thus supporting the *Parieto-Frontal Integration Theory* (Jung and Haier, 2007).

Finally, it was also described a relationship between cortical morphometry in frontal and parietal regions with some cognitive functions such as intelligence or creativity. Importantly, cortical morphometry proved to be a good correlate of cognitive abilities, as well as a good indicator of neural maturity. Some studies on non-gifted subjects have reported the existence of relationships between measurements of cortical thickness and surface area and high-level neuro-cognitive abilities such as IQ, g-factor, executive functioning, fluid reasoning or creativity (Burzynska, et al., 2012; Colom, et al., 2013; Fjell, et al., 2006; Fjell, et al., 2015; Jung, et al., 2010; Karama, et al., 2011; Luders, et al., 2009b; Narr, et al., 2007; Schnack, et al., 2014; Shaw, et al., 2006; Skranes, et al., 2013; Tamnes, et al., 2010a). Broadly speaking, these associations indicate that higher cognitive ability corresponds with lower cortical thickness and higher surface area. Furthermore, developmental studies suggested that during adolescence cortical thickness decreases and surface area increases (Aleman-Gomez, et al., 2013). Other cross-sectional and longitudinal studies reported different patterns of cortical maturation as a function of subject IQ (Schnack, et al., 2014; Shaw, et al., 2006). However, to our knowledge, the possible existence of cortical features that are specific to math-gifted individuals has not been explored.

2.3.4 Neuroimaging in Math-Gifted Subjects: A Gap in the Literature

Although ‘intelligence’ and other cognitive functions have been broadly studied with different neuroimaging modalities, the neuroimaging literature in math-giftedness was exclusively restricted to functional MRI studies. Despite the above mentioned studies of correlation between intellectual abilities (IQ, fluid reasoning, etc.) and Diffusion Tensor Imaging (DTI) or voxel-based morphometry (VBM), the white matter properties or the cortical features in math-gifted subjects are still largely unknown.

Focusing on math-gifted adolescents, previous neuroimaging studies supported that math-giftedness shows atypical brain functioning. Some authors supported the hypothesis of a unique pattern of activations while math-gifted subjects perform certain tasks. The high-level skills in math-reasoning suggested that math-gifted’s brain organization may be different from that of individuals who are not mathematically gifted (Alexander et al., 1996; Dehaene et al., 2003; Dehaene et al., 1999; O’Boyle et al., 2005; Prescott et al., 2010; Singh and O’Boyle, 2004). In this section we summarize the ‘state of the art’ about brain features in math-giftedness.

Math-gifted subjects show more developed right hemisphere (Benbow, 1986; Benbow and Lubinski, 1993; O'Boyle et al., 1991; O'Boyle et al., 2005; Prescott et al., 2010). These brains show enhanced development and activation of the right hemisphere, which in turn may confer higher performance in visuospatial processing capabilities (Geschwind and Galaburda, 1984; O'Boyle et al., 1991; O'Boyle et al., 1995) and arithmetic calculations (Pesenti et al., 2001). The right hemisphere is dominant for visuospatial and geometric analysis and is also involved in mathematical reasoning and creativity (Joseph, 1988). Michael O'Boyle and colleagues, in an EEG study, reported a reduction of alpha frequency band in the right hemisphere of math-gifted subjects while performing a cerebral laterality task (O'Boyle, et al., 1991). This alpha suppression is regarded as an indicator of brain 'activation'. In the same study, O'Boyle and colleagues (1991) reported also a correlation analysis showing that the greater the right hemisphere alpha suppression, the higher the capabilities in mathematical thinking. Furthermore, in other EEG study, Alexander and O'Boyle (1996) showed that the alpha power over the right hemisphere during rest in math-gifted children is greater than in average-ability and college-age subjects. The 'lower activity' under resting condition may reflect an unencumbered state such that these brain regions can be readily activated when cognitive processing is required, through greater decrease in alpha power (Alexander, et al., 1996). In agreement with these results, a Positron Emission Tomography (PET) study showed a positive correlation between cortical glucose metabolic rate and mathematical reasoning ability in temporal lobes; in this study the right hemisphere activation was greater than the left (Haier and Benbow, 1995). More recently, Prescott and colleagues (2010) using a functional MRI study showed that math-gifted subjects presented not only greater functional connectivity within the right hemisphere, but also greater connectivity between the left and the right hemisphere (Prescott, et al., 2010a).

Math-gifted subjects present a special form of bilateralism during information processing, which has been proposed as a key of math-giftedness (O'Boyle and Benbow, 1990). In a behavioral study, O'Boyle (1994) in order to study the dominant cerebral activity for basic information processing in math-gifted individuals used a finger-tapping paradigm. During the study, the subjects had to read out a paragraph loud, while they were asked to simultaneously tap a key-pad with the index finger of each hand (one hand at a time). Non-gifted individuals presented lower tapping rate of the right hand, which was affected by verbal processing of left hemisphere. However, math-gifted subjects

showed significantly reduced tapping rate of both left and right hands, suggesting similar engagement of both hemispheres during linguistic processing (O'Boyle, et al., 1994). The hypothesis of the special bilateral information processing in math-giftedness (O'Boyle, et al., 1994; Singh and O'Boyle, 2004) was also supported by different fMRI neuroimaging studies (Hoppe, et al., 2012; Lee, et al., 2006; O'Boyle, et al., 2005). These fMRI studies reported that math-gifted subjects activated an extended fronto-parietal network bilaterally, as well as an important activation of the anterior cingulate cortex (ACC). The functional bilateralism and the interplay between the frontal and parietal regions produce a unique characteristic of math-gifted brain (O'Boyle, et al., 2005). Singh and O'Boyle proposed that this functional bilateralism might be due to a well-developed corpus callosum (Singh and O'Boyle, 2004). However, although Prescott and other authors confirmed that math-gifted subjects present greater interhemispheric functional connectivity, there are no DTI studies to assess white matter properties of the structures that connect left and right hemispheres in math-gifted subjects. This enhanced interhemispheric information processing in math-gifted subjects and the greater involvement of the right hemisphere would promote the capacity of high-order cognition in math-giftedness. Some authors suggested that the activation of both hemispheres and interaction between them is essential for complex mathematical reasoning (Dehaene et al., 1999). The bilateral engagement of the fronto-parietal network provides to math-giftedness heightened processing capabilities and enhanced neuronal communication and integration of information during reasoning, imagery and creative thinking processes. Finally, in the last years, some EEG studies suggested that other of the brain features of math-giftedness is their highly adaptive reorganization of fronto-parietal network (Zhang, et al., 2014; Zhang, et al., 2015a; Zhang, et al., 2015b). Theoretically, a highly adaptive functional brain network benefits timely and effective information transfer, communication and processing, while facing external stimuli and inner perturbation. These studies revealed that, in different time intervals with millisecond precision, math-gifted subjects exhibited more extensive redistribution of fronto-parietal connections than average-ability subjects. The enhanced adaptiveness of dynamic reorganization makes the synchronizing network in the mathematically gifted brain (Zhang, et al., 2015a).

Summing up, the combination of a special form of bilateralism in the fronto-parietal network and enhanced functioning of the right hemisphere seem to be the neurobiological substrate of math-giftedness (Benbow, 1986; Benbow and Lubinski, 1993; Geschwind

and Galaburda, 1984; O'Boyle et al., 1991; O'Boyle et al., 1995). These characteristics involve heightened functional connectivity between the left and right hemispheres (Singh and O'Boyle, 2004). Although recently Prescott and cols (2010) described an enhanced functional connectivity in math-gifted adolescents, there are no studies on white matter microstructure in math-gifted subjects. These studies could confirm the greater structural connectivity between hemispheres and their link with their functional bilateralism. Moreover, at these days there are no studies published about the cortical characteristics in math-gifted subjects. Probably, one of the main reasons could be that neuroscientists have been interested in the impact of the intelligence (or IQ) on white and grey matter more than in any special giftedness. The above mentioned studies of neuroimaging suggest the interest of studying the brain features of math-gifted subjects. The next chapters present three neuroimaging studies, in which different brain characteristics of some math-gifted adolescents were analyzed.

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Chapter 3. Mathematically Gifted Adolescents Use More Extensive and more Bilateral Areas of the Fronto-Parietal Network than Controls during Executive Functioning and Fluid Reasoning Tasks

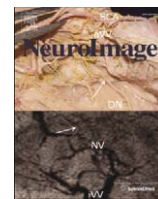
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Mathematically gifted adolescents use more extensive and more bilateral areas of the fronto-parietal network than controls during executive functioning and fluid reasoning tasks

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ABSTRACT

The main goal of this study was to investigate the neural substrates of fluid reasoning and visuospatial working memory in adolescents with precocious mathematical ability. The study population comprised two groups of adolescents: 13 math-gifted adolescents and 14 controls with average mathematical skills. Patterns of activation specific to reasoning tasks in math-gifted subjects were examined using functional magnetic resonance images acquired while the subjects were performing Raven's Advanced Progressive Matrices (RAPM) and the Tower of London (TOL) tasks.

During the tasks, both groups showed significant activations in the frontoparietal network. In the math-gifted group, clusters of activation were always bilateral and more regions were recruited, especially in the right hemisphere. In the TOL task, math-gifted adolescents showed significant hyper-activations relative to controls in the precuneus, superior occipital lobe (BA 19), and medial temporal lobe (BA 39). The maximum differences between the groups were detected during RAPM tasks at the highest level of difficulty, where math-gifted subjects showed significant activations relative to controls in the right inferior parietal lobule (BA 40), anterior cingulate gyrus (BA 32), and frontal (BA 9, and BA 6) areas. Our results support the hypothesis that greater ability for complex mathematical reasoning may be related to more bilateral patterns of activation and that increased activation in the parietal and frontal regions of math-gifted adolescents is associated with enhanced skills in visuospatial processing and logical reasoning.

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Introduction

The capacity for fluid reasoning, working memory, and mental imagery is considered to be fundamental for skilled mathematical reasoning (Gray et al., 2003; Lee et al., 2006). Mathematical thinking is associated with comprehension, understanding, and using patterns, as well as with organizing and systematizing our ideas to discover the rules that govern processes involving numbers. Fluid reasoning, working memory, and mental imagery are thought to be crucial for mathematical

thinking. Fluid reasoning is the ability to perceive complex relations and engage in working memory, concept formation, reasoning, and abstraction. Working memory makes it possible to retain and manipulate information from intermediate steps while solving a problem (Newman et al., 2003; Prabhakaran et al., 1997). Mental imagery is the ability to visualize mental images that are structurally similar to perceptions during reasoning in order to find new information not explicitly given in the premises; this ability makes it easier to clarify and understand data and the relationships between them. These relationships may be tangible (e.g., graphs, maps, or three-dimensional models) or mental (e.g., mental images that can be used during reasoning to find new information not explicitly given in the problem) (Knauff et al., 2002).

Results from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies suggest that fluid reasoning is associated with activation of a network of frontal and parietal brain

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regions, specifically the dorsolateral prefrontal cortex (DLPFC) (Brodmann area [BA] 9, 46) and the superior parietal lobule and intraparietal cortices (BA 7, 40) (Fincham et al., 2002; Lee et al., 2006; Newman et al., 2003; Smith and Jonides, 1999; Todd and Marois, 2004; van den Heuvel et al., 2003). These regions have been related to visuospatial and/or verbal working memory subsystems such as executive functioning, mental imagery (Harris et al., 2000; Just et al., 2001; O'Boyle et al., 2005), and control of spatial attentional shifts (Coull and Frith, 1998). Some researchers have suggested that fluid reasoning is highly dependent on working memory capacity (Fincham et al., 2002; Lee et al., 2006; Prabhakaran et al., 1997; van den Heuvel et al., 2003). Importantly, brain activation associated with fluid reasoning is dependent on the level of task difficulty. In other words, increasing task-related working memory load is associated with increased task-related brain activation in the DLPFC (Carpenter et al., 1990) and superior parietal lobules (Klingberg et al., 1997; Lee et al., 2006; Perfetti et al., 2009).

Math-gifted subjects show high-level skills in mathematical reasoning, and it has been suggested that their brain organization is different from that of individuals who are not mathematically gifted (Alexander et al., 1996; Dehaene et al., 2003; Dehaene et al., 1999; O'Boyle et al., 2005; Prescott et al., 2010; Singh and O'Boyle, 2004). Their brains show enhanced development and activation of the right hemisphere (Benbow, 1986; Benbow and Lubinski, 1993; O'Boyle et al., 1991, 2005; Prescott et al., 2010), which in turn confers higher specialization in visuospatial processing capabilities (Geschwind and Galaburda, 1984; O'Boyle et al., 1991, 1995) and arithmetic calculations (Pesenti et al., 2001). A special form of bilateralism (O'Boyle et al., 2005) and higher connectivity between the left and right hemispheres are also characteristic of math-gifted individuals (Alexander et al., 1996; Singh and O'Boyle, 2004). Activation of both hemispheres and interaction between them is essential for complex mathematical reasoning (Dehaene et al., 1999). In math-gifted subjects, we can study the neural substrate underlying high fluid reasoning and visuospatial working memory and how this overlaps with complex mathematical thinking. Two studies with math-gifted adolescents reported a bilateral frontoparietal network associated with fluid reasoning and visuospatial working memory (Lee et al., 2006; O'Boyle et al., 2005). Their results suggest that, when performing fluid reasoning (Lee et al., 2006) and mental imagery tasks (O'Boyle et al., 2005), math-gifted subjects showed a stronger recruitment of task-related brain areas.

The goal of our study was to investigate the neural substrates of fluid reasoning and visuospatial working memory in adolescents with precocious mathematical ability. We used fMRI to scan mathematically precocious adolescents and adolescents with average mathematical skills (controls) during Raven's Advanced Progressive Matrices (RAPM) and the Tower of London (TOL) tasks. These tests are considered good neuropsychological tests and are used together to assess fluid reasoning, visuospatial working memory, and executive function and planning (Alderton and Larson, 1990; Dagher et al., 1999). Based on previous research, we hypothesize that adolescents with precocious mathematical ability will show more bilateral activation and more areas recruited in the right hemisphere during the RAPM and the TOL tasks. This hypothesis would stand in contrast to what would be expected using an explanation based on neural efficiency. We believe that these distinctive activations could be associated with the level of task complexity.

Methods

Subjects

Two groups of adolescents were included in the study: math-gifted subjects and controls (Table 1).

Math-gifted subjects

This group was composed of 13 adolescents (8 males and 5 females aged 12–14 years, mean 13.8 years, SD = 0.6) with precocious mathe-

Table 1

Mean and standard deviation (SD) of demographic data for each group.

	Controls (n = 14)		Math-gifted (n = 13)		p*
	Mean	SD	Mean	SD	
Age	13.4	0.8	13.8	0.6	
Gender (male/female)	9/5		8/5		
Education (yr)	7.7	0.6	7.8	0.7	
Handedness (right/left/mixed)	14/0/0		14/0/0		
Estimated Full-Scale IQ	90.0	18.1	130.8	10.7	<0.001
Verbal IQ	98.1	17.1	125.1	12.1	<0.001
Performance IQ	84.3	26.5	128.8	12.1	<0.001

*Student *t*-test of differences between groups.

matical ability and an estimated Full-Scale Intelligence Quotient FSIQ of 130.7 (SD = 10.7) (Table 1). They had a mean of 7.8 years' formal education (SD = 0.7) and were enrolled in the *Stimulus of Mathematical Talent Program* (ESTALMAT¹—“Programa de Estimulo del Talento Matemático”) of the Spanish Royal Academy of Mathematical, Physical and Natural Sciences in Madrid.

ESTALMAT is an extracurricular program aimed at the stimulus of mathematical thinking by engaging participants in mathematical games oriented and supervised by mathematics professors from the Universidad Autónoma de Madrid. To enter the program, subjects first underwent a screening process at school and took a specific ESTALMAT test designed by expert mathematicians. The objective of the test was to detect the 6 complex mathematical abilities proposed by Kiesswetter (Heller et al., 2000): 1) organizing materials; 2) recognizing patterns or rules; 3) changing the representation of the problem and recognizing patterns and rules in this new area; 4) comprehending and working with highly complex structures; 5) reversing and inverting processes; and 6) finding related problems. To pass the test, responses were examined by mathematicians taking into account not only whether the responses were correct, but also the argumentation followed to achieve the solution. In comparison with other standardized measures such as SAT-Math, ESTALMAT emphasizes mathematical problem solving by creative thinking, rather than using concepts and previous expertise gained at school.

Controls

The control group was recruited from the same schools as the math-gifted group within the autonomous region of Madrid. This group was composed of 14 adolescents (9 males and 5 females). They had the average mathematical ability of children of their school grade. Mean estimated FSIQ was 90 (SD = 18.1), and they were matched with the math-gifted group for age (mean 13.4 years, SD = 0.8), sex, and years of education (mean 7.7 years, SD = 0.6) (Table 1).

The selection process for control subjects involved an initial telephone interview to confirm suitability (i.e. age, sex, parental consent, availability, and basic exclusion criteria). The inclusion criteria were age 12–14 years, right-handedness, Spanish as the first language, and at least 5 years' schooling in the Spanish education system. Handedness was determined in all subjects using item # 5A, of the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989).

Exclusion criteria

For all subjects, the exclusion criteria were illness (medical, neurological, or psychiatric), history of head injury with loss of consciousness, presence of metallic implants or body tattoos, orthodontic appliances, pervasive developmental disorders, and pregnancy or breast-feeding. To rule out subjects with atypical cognitive functioning and mental retardation, overall intellectual functioning was estimated using the Vocabulary, Information, and Block Design subtests from the Spanish

¹ <http://www.uam.es/proyectosinv/estalmat/>.

version of the Wechsler Intelligence Scale for Children – Revised (WISC – R). This short form of the IQ was estimated from these 3 subtests following (Ringe et al., 2002; Silverstein, 1985) and showed a good correspondence with FSIQ (Satler, 2001). The cognitive assessment, which was intended to rule out abnormal intellectual functioning, was performed by a child neuropsychologist and a child psychiatrist, taking into account the performance in the TOL and RAPM tasks and school records.

Controls were recruited to match math-gifted subjects for age and academic level, but not explicitly by IQ, since this may induce a bias, and the control group would not be any longer representative of the mathematically average population. Thus, it is reasonable to expect a higher dispersion of IQ among controls than in math-gifted subjects, as no low-IQ children are likely to present math abilities (Table 1).

The study was approved by the Ethics and Clinical Research Boards of the Gregorio Marañón General Hospital. Written informed consent was obtained from the parents and subjects before the study began.

Experimental paradigms

Executive functioning task

For the executive functioning and visuospatial working memory and mental imagery assessment, we used the Tower of London (TOL) protocol as in previous studies, where individuals were asked to plan how to move three differently colored balls arranged in three boxes of unequal length in order to match a target position with the minimum number of moves (Newman et al., 2003). The degree of difficulty was adjusted by selecting the minimal number of moves required to solve a problem (path length to solution varied between 2 and 5 moves). Within each activation block, difficult and easy trials were randomly presented, so that all the activation blocks in this task had the same working memory load.

As a control task, we used the same setting, but the start and end configurations were identical; therefore, the number of moves was zero (Fig. 1). This control task was designed to require similar processing in terms of visual stimulus encoding, decision process, and motor response execution, without the need for reasoning.

Fluid reasoning task

Fluid and analytical reasoning was assessed using Raven's Advanced Progressive Matrices (RAPM). During this task, participants were asked

to choose the missing pattern in a series of 3×3 matrices of figures with the bottom right figure missing (Raven, 1965). We simplified our version in such a way that the subject had to select the missing figure from four candidate options (instead of the standard number of 8) presented below the matrix. Items in the RAPM task were progressively more difficult and required increasing cognitive capacity to encode and analyze the task. The control task for this experiment was a 3×3 matrix of identical figures with the bottom right figure missing. Participants did not have to identify a relationship between the figures, as they were all identical. Thus, the same processes involved in the test condition were required by this task, except for reasoning (Fig. 1).

fMRI imaging procedure

Data were acquired on a Philips Intera 1.5T MRI scanner. For each participant, a high-resolution structural T1 image was initially acquired (gradient-echo; TR = 25 ms; TE = 9.2 ms; matrix size = $256 \times 256 \times 175$; flip angle = 30° ; slice thickness = 1 mm; and voxel size $1 \times 1 \times 1$ mm m).

The fMRI study used a T2*-weighted echo-planar sequence with the following parameters: TR = 3000 ms, TE = 50 ms, matrix size = $64 \times 64 \times 20$; flip angle = 90° , voxel size 3.6×3.6 mm; slice thickness = 5 mm; and 20 axial slices. For each task, the fMRI acquisition lasted 7 min and 30 s (150 functional images, one every 3 s).

fMRI Protocol

In both tasks, the fMRI paradigm involved the presentation of slides for each task. Upon display, subjects were carefully instructed and trained to respond by pressing one of four buttons (corresponding to the right thumb, index, middle, and ring fingers) to indicate which of the four options represented the correct response (Fig. 1). After pressing a button, a new task slide was presented. Response time was the length of time between appearance of the slide and response. The maximum response time allowed was 20 s, after which the next slide appeared automatically. Inability to complete a slide was recorded as "missing response". In each run, baseline and activation blocks were alternatively presented in this fashion: 9 control slides as the baseline block, and 4 task slides as the activation block. For the RAPM and TOL exercises, blocks were alternated for 7 min 30 s (fMRI sequence time). Therefore, since the course of the paradigm was self-paced, the number of activation blocks and the total number of task slides varied across subjects and

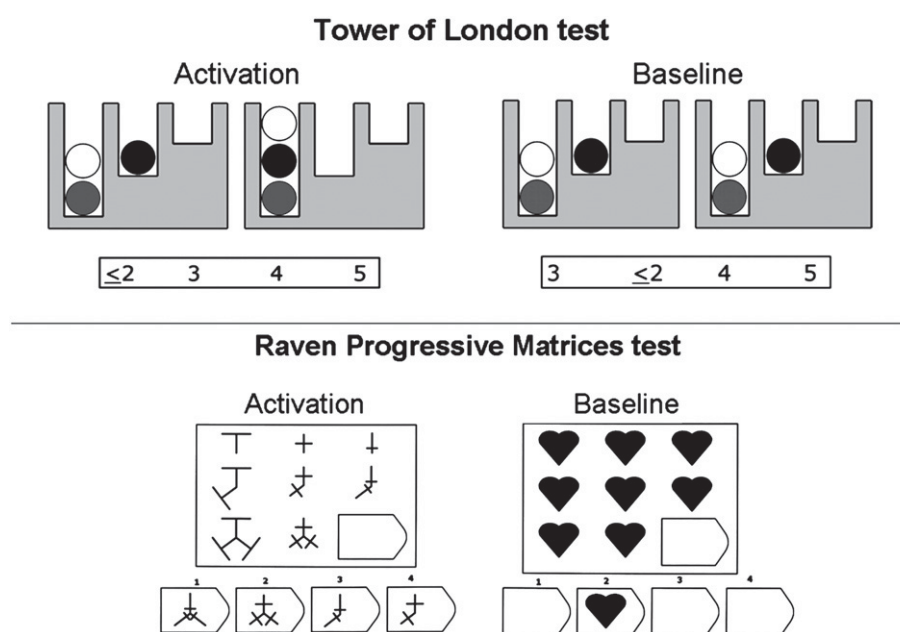


Fig. 1. Examples of activation and baseline trials in the TOL and RAPM tasks. Subjects selected the correct response by pressing one of four available buttons.

tasks due to a faster or slower response time. Full details of the number of slides and time spent on each task in the TOL are provided in Table 2.

In order to compare difficult with easy trials in the RAPM paradigm, the level of complexity was increased progressively from one block to the next, and also within each block. The first three activation blocks (12 slides) were considered “easy blocks”; the subsequent slides were considered “difficult blocks”. Since the trials in the RAPM booklet (Raven, 1965) are presented by increasing complexity, difficult trials were chosen from those appearing at the end. In the TOL task, difficulty level effects were not assessed, because in all the activation blocks, difficult and easy trials were randomly presented.

The number of slides presented in the TOL was significantly larger in controls ($P=0.0246$). However, no significant differences between the groups were observed in the accumulated display time (Table 2). The number of baseline and activation blocks for each task was similar in both groups. The RAPM task was run first; the TOL was started after a 3-min rest. Number of slides presented in RAPM was significantly larger in difficult than in easy trials in both math-gifted subjects ($P=0.0012$) and controls ($P<0.0001$) (Table 2). The amount of time spent solving task slides was also significantly larger in difficult than in easy trials in both math-gifted subjects ($P<0.0001$) and controls ($P<0.0001$) (Table 2).

All participants had a practice session with both the TOL and the RAPM tasks before entering the scanner, and a neuropsychologist made sure they had correctly understood the tasks. These examples were not used during the acquisition. Test performance was also recorded for each subject. The variables used to assess performance were response time and percentage of correct responses.

Data analysis

To study task performance, the number of correct responses and the reaction time for correct and incorrect responses was recorded. Differences between groups were tested using the t test.

The fMRI data were pre-processed following the standard protocol of Statistical Parametric Mapping (SPM5; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). To control for drift, EPI volumes were realigned within subjects to the first image in the series using a rigid transformation (6 parameters). Results were visually checked and no subject had to be excluded using a criterion of 2 mm of displacement. The images were then normalized to the standard SPM5 MNI EPI template. Normalization parameters were estimated using the mean image for each run and these were applied to all volumes of that run. A linear affine transformation was applied followed by non-linear deformations using the SPM5 default parameters. Normalized images were spatially smoothed with an 8 mm³ full width half maximum (FWHM) Gaussian kernel.

Statistical analysis was based on a general linear model in a block-design analysis. Effects and significance were assessed voxelwise using linear contrasts (t test). Contrast images for the individual subjects were first analyzed within-subject and within-group (first-level) and then between-group (second-level). Gender-effects were not included in the

model because the sample size was too small for testing the group*gender interaction. Nevertheless, the gender ratio was similar in both groups (Table 1). To correct for multiple comparisons, we used the familywise error (FWE) criteria, and statistical maps were assessed for voxelwise significance using an FWE voxel and cluster threshold of $P=0.001$. The between-group comparison analyses (math-gifted>control group) were thresholded using an FWE-corrected P value of 0.05 combined with a cluster size threshold of 10 voxels. Where indicated, parameter estimates were extracted from group comparisons and reported for each group separately. Differences between groups were compared using a random-effects model and two-sample t test contrasts for math-gifted vs. controls, and, in the case of RAPM tasks, for easy vs. difficult. For the contrasts of easy vs. difficult, we used a less conservative voxel- and cluster-level threshold ($P<0.001$ uncorrected), because this analysis was made including the effect size images resulting from the first-level analysis instead of the raw data for each subject. For this reason, the degrees of freedom are reduced in this comparison.

To rule out possible confounding effects derived from the differences in IQ observed between groups, we conducted three additional analyses performed separately for TOL and RAPM tasks (see Supplementary Results). First, a correlation between estimated FSIQ and effect size of task activation vs. baseline. This analysis shows that only a few clusters had significant correlations with FSIQ (see Supplementary Results). The second analysis was a repetition of the within-group test of activation vs. baseline, but including estimated FSIQ in the model as a covariate. The model with covariate yielded similar results to those of the model with no covariate in both controls and math-gifted subjects (see Supplementary Results). The third test was a ROI analysis of specific brain regions intended to replicate our voxel-wise results with ROI data. This ROI analysis was performed to test for significant differences in activation vs. baseline using an ANOVA or ANCOVA model with FSIQ as covariate. The ROIs selected were the left middle frontal gyrus and the right superior occipital gyrus. These ROIs were part of the clusters showing group differences and significant activations related to the task (Tables 5 and 6). In both regions, between-group differences were similar in the model with or without covariate (see Supplementary Results).

To locate anatomical structures, voxel coordinates of significant clusters were transformed from MNI space into Talairach space by non-linear transformations based on the “mni2tal” script by MATLAB 7 (Mathworks Inc., USA) and the TalDaemon reference (www.talairach.org). Figures showing statistical maps were superimposed on anatomical renders of SPM5 and on anatomic images using MRIcron software (<http://www.cabiatl.com/mricro/mricron/index.html>).

Results

Task performance

Overall, both groups showed similar values for behavioral measures in both tasks.

Table 2
Mean and standard deviation (SD) of behavioral data for each group during the TOL and RAPM tasks.

	Tower of London				P^*	Raven Advanced Progressive Matrices				P^*
	Math-gifted (n = 13)		Control (n = 14)			Math-gifted (n = 13)		Control (n = 14)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Correct response (%)	75.8	12.4	64.1	17.4	–	66.9	12.6	51.0	13.4	0.0042
Reaction time	10.4	2.0	10.7	2.0	–	10.9	2.4	10.3	1.8	–
Reaction time correct response	9.6	1.7	9.4	1.7	–	10.2	2.2	8.9	1.7	–
Reaction time failed response	4.1	2.3	6.2	2.5	0.0363	8.2	2.6	8.9	1.7	–
Activation trials completed	24.2	7.3	26.6	6.3	0.0246	31.2	7.7	34.0	5.7	–
Accumulated display time	239.7	34.0	273.7	39.3	–	328.1	56.8	342.2	29.2	–
Missing responses	2.2	0.8	3.4	1.6	–	2.4	1.6	2.7	0.9	–

* P value, Student t test of differences between groups.

Group differences

In the TOL task, only the reaction time of incorrect responses was significantly shorter in the math-gifted subjects ($P = 0.0363$). In the RAPM task, only the percentage of correct responses was significantly higher in the math-gifted subjects ($P = 0.0042$) (Table 2). Regarding task difficulty, group differences were only observed in difficult tasks, and the percentage of correct responses was significantly higher in math-gifted subjects than in controls ($P = 0.0009$).

Differences between complexity levels within groups

Reaction time increased with complexity in both the math-gifted group ($P = 0.0237$) and the control group ($P = 0.0204$), thus confirming that subjects were truly engaged in the test. The reaction time for correct responses was significantly higher in difficult than in easy tasks in both math-gifted subjects ($P = 0.0028$) and controls ($P = 0.0141$). Only the controls showed differences in task performance, namely, the percentage of correct responses was significantly lower in difficult tasks than in easy ones ($P = 0.0015$) (Table 3).

Tower of London task

During the TOL task, significant activation was observed in the frontal, temporal, and parietal lobes. The math-gifted group showed clusters of activation (relative to baseline) that were always bilateral and with more regions activated than the control group (Table 4, Fig. 2). Previous fMRI studies during TOL in normal subjects showed activations in the prefrontal cortex and parietal cortices (Boghi et al., 2006; Fincham et al., 2002; Lazeron et al., 2000; Newman et al., 2003; Wagner et al., 2006), thus supporting the validity of our TOL paradigm.

Math-gifted subjects

Bilateral activation was seen in the precuneus (BA 7/19 and BA 31 on the right hemisphere), premotor cortex at the superior frontal gyrus (BA 6), superior parietal lobule (BA 7), inferior parietal lobule (BA 40), ventrolateral prefrontal cortex (VLPFC) at the inferior frontal gyrus (BA 47), and rostralateral prefrontal cortex (RLPFC) at the middle frontal gyrus (BA 10). Activation in the left hemisphere only was observed in the superior occipital gyrus and middle temporal gyrus (BA 19), middle occipital gyrus (BA 18/19), cuneus (BA 18), and RLPFC at the inferior and superior frontal gyri (BA 10). Activation affecting the right hemisphere only was observed in the postcentral gyrus (BA 7), premotor cortex at the middle frontal gyrus (BA 6), DLPFC at the middle frontal gyrus (BA 9/46), and inferior temporal gyrus (BA 20) (Table 4, Fig. 2).

Controls

Bilateral activation was observed in the precuneus (BA 7), superior parietal lobule (BA 7), cuneus (BA 18), middle occipital gyrus (BA 18), premotor cortex at the superior and middle frontal gyri (BA 6, BA 8 on the left hemisphere), and VLPFC at the inferior frontal gyrus (BA 47).

Activation in the left hemisphere only was observed in the supramarginal gyrus and inferior parietal lobule (BA 40), superior temporal gyrus (BA 13), inferior temporal gyrus (BA 37), DLPFC at the inferior frontal gyrus (BA 46/9), and cingulate gyrus (BA 32). Activation in the right hemisphere only was observed in the postcentral gyrus (BA 7) (Table 4, Fig. 2).

Between-group analysis

In the between-group analysis (math-gifted > controls), the math-gifted adolescents showed activations in the right superior occipital gyrus (BA 19), right precuneus (BA 19), and bilateral medial temporal gyrus (BA 39) (Table 5, Fig. 3a). Considering that both BA 19 and BA 39 correspond to the associative cortex, the cluster showing significant differences on the left temporal gyrus (BA 39) is anatomically located within the largest within-group activation cluster observed in math-gifted subjects, labeled as the middle temporal gyrus (BA 19) in Table 4.

Raven's Advanced Progressive Matrices

During the RAPM task, significant activations were observed in the frontal, parietal, and temporal lobes. The math-gifted group showed a more extensive and bilateral pattern of activations including more regions than the control group (Table 6, Fig. 4). Previous fMRI studies during performance of RAPM for the evaluation of fluid reasoning and working memory in normal subjects had revealed activations in the frontal and parietal cortices (Christoff et al., 2001; Gray et al., 2003; Kroger et al., 2002; Masunaga et al., 2008; Perfetti et al., 2009; Prabhakaran et al., 1997; Wendelken et al., 2008). These studies showed that the frontoparietal network is active in both hemispheres during tasks that require working memory, such as TOL and RAPM, and their results support the validity of our RAPM paradigm.

Math-gifted subjects

Bilateral activation was seen in the middle occipital gyrus (BA 18/19), precuneus (BA 7, BA 19 on the left hemisphere), superior parietal lobule (BA 7), inferior parietal lobule (BA 40), premotor cortex at the middle frontal gyrus (BA 6), and DLPFC at the inferior frontal gyrus (BA 46, BA 9 on the left hemisphere). Activation on the left hemisphere only was seen in the cuneus (BA 19), premotor cortex at the middle frontal gyrus (BA 6), DLPFC at the inferior frontal gyrus (BA 9), and RLPFC at the superior, middle and inferior frontal gyri (BA 10). Activation on the right hemisphere only was seen in the superior occipital gyrus (BA 19), fusiform gyrus (BA 37), and VLPFC at the inferior frontal gyrus (BA 44) (Table 6, Fig. 4).

Controls

Bilateral activation was seen in the cuneus (BA 18), middle occipital gyrus (BA 18 plus BA 19 on the left hemisphere), and superior parietal lobule (BA 7). Activation in the left hemisphere only was seen in the precuneus (BA 7) and DLPFC at the middle frontal gyrus (BA 46/9). Right

Table 3
Mean and standard deviation (SD) for behavioral measures in each group and complexity level during the RAPM task.

	Raven's Advanced Progressive Matrices											
	Math-gifted (n = 13)				Control (n = 14)				Group ^a		Difficulty ^b	
	Easy		Difficult		Easy		Difficult		Easy	Difficult	Math-gifted	Control
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Correct response (%)	69.2	15.2	65.4	13.8	64.9	15.7	43.7	15.9	–	0.0009	–	0.0015
Reaction time	9.3	2.9	11.9	2.6	9.1	1.7	11.0	2.2	–	–	0.0237	0.0204
Reaction time correct response	8.1	2.9	11.4	1.9	7.7	1.9	9.9	2.4	–	–	0.0028	0.0141
Reaction time failed response	8.5	4.2	8.3	3.3	9.2	2.6	9.3	2.0	–	–	–	–
Activation trials completed	11.7	0.5	19.5	7.7	12.0	0.0	22.0	5.7	–	–	0.0012	<0.001
Accumulated display time	108.2	32.9	219.9	73.6	109.6	20.6	232.6	36.2	–	–	<0.0001	<0.001
Missing responses	1.5	0.8	1.9	0.8	1.6	1.3	1.9	0.7	–	–	–	–

^a P value, student *t* test between groups for each complexity level.

^b P value, student *t* test between complexity levels for each group.

Table 4
 Results of the first-level analysis for the math-gifted and control groups during the Tower of London task. Anatomical regions with significant activations compared to baseline, hemisphere (R, right; L, left), Brodmann area (BA), local maxima coordinates in Talairach space (mm), Z-score, and cluster size (k). The table only reports the t values higher than t >4.7. Cluster-level significance P corrected <0.001 (Cluster size > 10 voxels); Voxel level significance: P FWE corrected <0.001. Boldfaced: P FWE <0.05; DLPFC, dorsolateral prefrontal cortex; RLPFC, rostralateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

Tower of London Test (activation>baseline)										
Region of significant activation		Math-gifted (n = 13)					Controls (n = 14)			
		Local Maxima					Local Maxima			
		Side	BAs	(x, y, z) mm	Z-score	k	BAs	(X, Y, Z) mm	Z-score	k
Frontal	Premotor cortex; Middle frontal gyrus	L					6\8	(-26, 11, 55)	>7.23	1008
		R	6	(28, 13, 58)	>7.65	1655	6	(28, 12, 51)	>7.23	1158
	Premotor cortex; Superior frontal gyrus	L	6	(-22, 11, 55)	>7.65	1772	6\8	(-22, 22, 51)	6.22	1008
		R		(24, 5, 64)	>7.65	1655	6	(26, 7, 62)	>7.23	1158
	DLPFC; Inferior frontal gyrus	L				9\46	(-55, 30, 15)	7.23	29	
	DLPFC; Middle frontal gyrus	R	9\46	(48, 40, 28)	>7.65	268				
	RLPFC; Inferior frontal gyrus	L	10	(-44, 50, -1)	>7.65	210				
	RLPFC; Middle frontal gyrus	L	10	(-34, 59, 12)	7.46	210				
		R		(44, 52, -7)	6.66	120				
	RLPFC; Superior frontal gyrus	L	10	(-40, 51, 18)	5.67	210				
VLPFC; Inferior frontal gyrus	L	47	(-51, 40, -7)	6.21	210	47	(-22, 18, -21)	>7.23	58	
	R		(20, 25, -4)	6.08	151		(24, 20, -23)	6.31	53	
Parietal	Precuneus	L	7\19	(-10, -63, 53)	>7.65	14712	7	(-8, -63, 51)	>7.23	7683
		R	7\19\31	(8, -65, 53)	>7.65	14712		(6, -58, 49)	>7.23	7683
	Postcentral gyrus	R	7	(12, -57, 65)	>7.65	14712	7	(12, -55, 63)	>7.23	7683
	Superior parietal lobule	L	7	(-24, -57, 56)	>7.65	14712	7	(-36, -55, 60)	5.67	7683
		R		(34, -60, 49)	>7.65	14712		(22, -63, 58)	>7.23	7683
	Supramarginal gyrus	L					40	(-38, -45, 33)	7.21	201
Inferior parietal lobule	L	40	(-46, -48, 48)	>7.65	14712	40	(-49, -46, 46)	5.01	201	
	R		(36, -39, 39)	>7.65	14712					
Occipital	Superior occipital gyrus	L	19	(-32, -82, 39)	>7.65	14712				
	Middle occipital gyrus	L	19\18	(-34, -77, 22)	>7.65	14712	18	(-28, -97, 5)	>7.23	402
		R						(20, -99, 7)	6.88	304
	Cuneus	L	18	(-26, -97, 1)	6.25	14712	18	(-14, -103, 7)	6.55	402
	R						(24, -95, 3)	>7.23	304	
Temporal	Superior temporal gyrus	L					13	(-38, -47, 26)	5.96	201
	Middle temporal gyrus	L	19	(-49, -79, 11)	6.38	14712				
	Inferior temporal gyrus	L					37	(-55, -57, -6)	5.85	48
		R	20	(55, -51, -13)	5.80	29				
	Parahippocampal gyrus	L	19	(-30, -47, -6)	5.75	36				
Cingulate gyrus	L					32	(-8, 25, 41)	6.96	71	

hemisphere activation only was seen in the middle and inferior occipital gyrus (BA 18), fusiform gyrus (BA 37), and DLPFC at the inferior frontal gyrus (BA 46) (Table 6, Fig. 4).

Between-group analysis

Group comparison of activation patterns relative to baseline in the easy tasks showed that the math-gifted group had significant activations in two regions of the right hemisphere: the postcentral gyrus (BA 2) and the inferior parietal lobe (BA 40) (Table 7; Fig. 3b).

The *Difficult>Easy* contrast showed significant results only in the math-gifted group, with higher bilateral activations in the middle occipital gyrus and cuneus (BA 18, 19) and DLPFC at the middle frontal gyrus (BA 9). In the right hemisphere, significant clusters were observed in the inferior parietal lobe (BA 40), anterior cingulate gyrus (BA 32), and the premotor cortex at the medial frontal gyrus (BA 6) (Table 7, Fig. 5). In the controls, no region showed differences while performing difficult tasks relative to easy tasks.

The *Math-gifted>Controls* contrast revealed significantly higher activations only while performing difficult tasks. The most significant differences in activation between the groups appeared in the right hemisphere, in the inferior parietal lobule (BA 40), postcentral gyrus (BA 2), and premotor cortex (BA 6) (Table 7, Fig. 5). No areas showed higher activations in controls than in math-gifted subjects during both difficult and easy tasks.

Discussion

During the resolution of the TOL and RAPM tasks, math-gifted adolescents showed a more extensively distributed pattern of frontoparietal

activation, with greater bilateralism and greater activation of the right hemisphere than the controls. The frontoparietal network responsible for fluid reasoning and visuospatial working memory is common to both groups. There are differences in neural activity between groups, and these differences are clearly seen when task complexity is considered in the comparisons: only activations during difficult tasks showed that the extension of the frontoparietal network is larger in math-gifted subjects, especially in the right hemisphere. Furthermore, differences between the groups in behavioral performance were only observed in difficult RAPM trials. Indeed, when the effect of the complexity on RAPM was tested, only the math-gifted group showed a significant increase in activations.

To our knowledge, the present study is the first fMRI study with a group of math-gifted adolescents assessed during the performance of both the TOL and RAPM tasks. These paradigms enable us to study complex cognitive processes, such as fluid reasoning, mental imagery, and visuospatial working memory, in a very special sample composed of carefully selected math-gifted adolescents and controls. The larger extension of the frontoparietal network activations observed in math-gifted adolescents during both tasks support the Parieto-Frontal Integration Theory (P-FIT) of intelligence (Jung and Haier, 2007). Activation in the math-gifted group covered more regions with greater bilateralism than in the controls, an observation that is consistent with the results of other authors (O'Boyle et al., 2005; Prescott et al., 2010). However, our results are inconsistent with those of Lee et al. (2006), who suggested that superior intellectual ability may not be due to recruitment of additional brain regions (Lee et al., 2006). Perfetti et al. (2009) found similar results with a sample of high-IQ subjects, postulating that the frontoparietal network is independent of

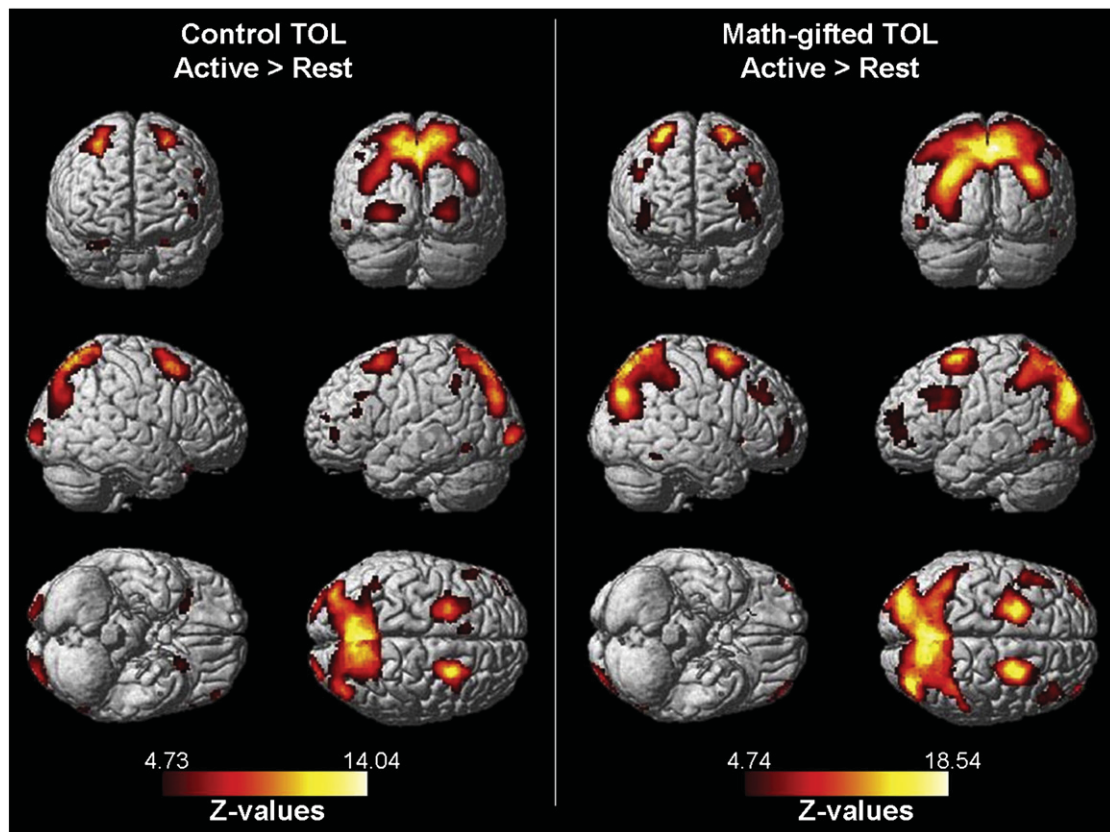


Fig. 2. First-level analyses in math-gifted and control groups during the TOL task. The clusters showing significant activations are color-coded for each group. Significant clusters are superimposed on the anatomical render (SPM5). The color bar shows the z-score for each group. More activation and bilateralism were observed in the frontal, prefrontal, and parietal cortices in math-gifted adolescents.

intellectual ability (high or low IQ) (Perfetti et al., 2009). In our study, the extent of activations and recruitment of new areas differed when the subjects were performing difficult trials, which may be interpreted as reflecting the functional specialization of math-giftedness.

In the frontoparietal activations common to both groups, some areas are associated with the type of task. The regions involved in making a decision and responding to a problem are the inferior and medial frontal gyri (BA 9/46, 44, and 47), which are known to support cognition during working memory and problem solving of differing types (deductive, and analogical). The DLPFC (BA 9/46) is the executive center of maintenance and information processing with internal representations during working memory, and a key brain region supporting reasoning and novel problem solving (Baker et al., 1996; Courtney et al., 1998; Chafee and Goldman-Rakic, 1998; Goldman-Rakic, 1987, 1995; Kroger et al., 2002; Lee et al., 2006; Owen et al., 1996; Perfetti et al., 2009; Todd and

Marois, 2004). Other frontal areas, such as the RLPFC and premotor cortex have been shown to support relational complexity and planning, respectively (BA 10 and 6) (Christoff et al., 2001; Kalbfleisch et al., 2007; van den Heuvel et al., 2003). In the premotor cortex, the role of BA 6 in higher-level cognition has been investigated in relationship to working memory (Owen et al., 1996; Smith and Jonides, 1999), updating spatial information (Tanaka et al., 2005), processes of attention, saccadic eye movements, and visuospatial manipulation processes (Brown et al., 2004; Courtney et al., 1998; Curtis and D'Esposito, 2003; Curtis et al., 2004; Smith and Jonides, 1999).

The posterior parietal cortex areas (BA 7, 19, and 40) store representations of visual information and are associated with spatial stimuli

Table 5

Between-group analysis, math-gifted>controls contrast. Anatomical regions with significant activation during the Tower of London task, hemisphere (R, right; L, left), Brodmann area (BA), local maxima coordinates in Talairach space (mm), Z-score, and cluster size (k). Significant differences in regions of activation between the two groups during TOL task ($t > 3.20$) are shown. Cluster-level significance P corrected < 0.01 (cluster size > 10 voxels). Voxel-level significance P uncorrected < 0.001 .

Towers of London (Math-gifted>Controls)					
Region of significant activation	Hemisphere	BAs	Local Maxima		
			(x, y, z) mm	Z-score	k
Superior occipital gyrus	R	19	(32, -76, 26)	4.30	183
Precuneus	R	19	(34, -72, 33)	3.62	183
Middle temporal gyrus	L	39	(-32, -69, 24)	4.21	134
	R	39	(34, -65, 25)	3.36	183

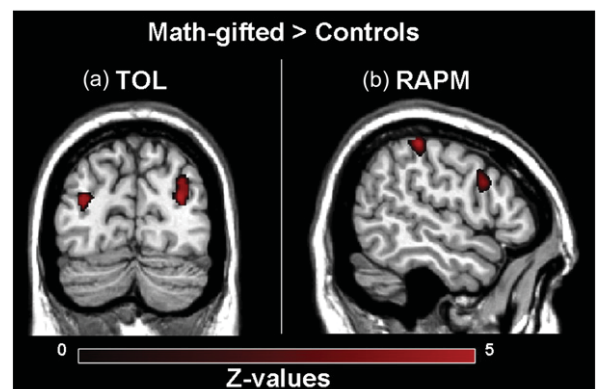


Fig. 3. Regions with significantly greater activation in math-gifted adolescents during the TOL (a) and RAPM (b) tasks than in controls (between-groups analyses; math-gifted>control group contrast) superimposed on the anatomical image; a) is in neurological orientation (left is left); b) is the right hemisphere.

Table 6
Results of the first-level analysis for the math-gifted and control groups during the Raven Advanced Progressive Matrices task. Anatomical regions with significant activations compared to baseline, hemisphere (R, right; L, left), Brodmann area (BA), local maxima coordinates in Talairach space (mm), Z-score, and cluster size (k). Only t-values higher than $t > 4.7$ are shown. Cluster-level significance P corrected < 0.001 (cluster size > 10 voxels); Voxel level significance P FWE corrected < 0.001 . Boldfaced: P FWE < 0.05 ; DLPFC, dorsolateral prefrontal cortex; RLPFC, rostralateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

Raven's Advanced Progressive Matrices (activation > baseline)										
Region of significant activation		Math-gifted (n = 13)					Controls (n = 14)			
		Local maxima					Local maxima			
		Side	BAs	(x, y, z) mm	Z-score	K	BAs	(x, y, z) mm	Z-score	k
Frontal	Premotor cortex; Middle frontal gyrus	L	6	(-26, 6, 49)	>7.76	2345				
		R		(30, 9, 57)	7.47	246				
	DLPFC; Inferior frontal gyrus	L	9	(-44, 3, 29)	>7.76	2345				
		R					46	(55, 38, 13)	6.62	52
	DLPFC; Middle frontal gyrus	L	9\46	(-44, 26, 17)	>7.76	2345	9\46	(-53, 19, 30)	5.88	207
		R	46	(53, 36, 22)	>7.76	108				
	RLPFC; Inferior frontal gyrus	L	10	(-46, 48, -4)	7.65	96				
	RLPFC; Middle frontal gyrus	L	10	(-36, 57, 7)	5.58	48				
	RLPFC; Superior frontal gyrus	L	10	(-30, 58, -4)	5.10	48				
VLPFC; Inferior frontal gyrus	R	44	(51, 9, 22)	>7.76	213					
Parietal	Precuneus	L	7\19	(-26, -76, 40)	>7.76	4048	7	(-22, -70, 40)	>7.73	1664
		R	7	(22, -71, 53)	>7.76	4048				
	Superior parietal lobule	L	7	(-28, -50, 41)	>7.76	4048	7	(-26, -71, 46)	>7.73	1664
		R		(26, -60, 40)	>7.76	3644		(28, -71, 44)	6.83	485
	Inferior parietal lobule	L	40	(-38, -46, 41)	>7.76	4048				
		R		(42, -42, 48)	7.15	3644				
Occipital	Superior occipital gyrus	L					19	(-32, -80, 26)	6.98	1664
		R	19	(34, -78, 29)	>7.76	3644				
	Middle occipital gyrus	L	18\19	(-34, -91, 2)	>7.76	4048	18	(-32, -87, 4)	7.41	1664
		R		(36, -89, -1)	>7.76	3644	18\19	(34, -87, 4)	>7.73	584
	Inferior occipital gyrus	R	18	(28, -91, -3)	>7.73	584				
Cuneus	L	19	(-30, -84, 24)	>7.76	4048	18	(-8, -100, 12)	7.09	180	
Temporal	Fusiform gyrus	R						(12, -94, 21)	6.08	95
		R	37	(49, -57, -9)	>7.76	418	37	(-48, -53, -8)	6.18	124

and processing task complexity (Champod and Petrides, 2007; Dehaene et al., 2003; Knauff et al., 2002; Lee et al., 2006; Newman et al., 2003; Perfetti et al., 2009; Prabhakaran et al., 1997; Todd and Marois, 2004; van den Heuvel et al., 2003). Both groups showed greater recruitment of the parietal cortices for both tasks. TOL and RAPM are both complex cognitive tasks that require visuospatial and abstract information processing.

Executive functioning

To solve the TOL test, subjects need planning ability, visuospatial working memory, and mental imagery. The level of complexity was not studied in this paradigm. The design focused on the pattern of activation compared to baseline, and the neural substrate of visuospatial working memory was assessed.

The activation patterns of both groups were similar, although the math-gifted group presented a much more extensive activation pattern, especially in frontal regions (premotor cortex, DLPFC, and RLPFC) and in the intraparietal sulcus, mostly in the right hemisphere.

The intraparietal sulcus plays a key role in processing representations of objects in space (Brown et al., 2004; Courtney et al., 1998; Curtis et al., 2005) and during numerical processing in adults (Dehaene et al., 2003). In addition, a correlation between visuospatial working memory capacity and intraparietal sulcus activity has been described (Todd and Marois, 2004). This finding suggests a greater visuospatial capacity in math-gifted adolescents. Our sample included males and females in a similar gender ratio in both groups. Possible gender effects on visuospatial processing (Boghi et al., 2006) were not assessed due to insufficient sample size.

The prefrontal cortex showed clear group differences in activation patterns. The DLPFC was active bilaterally in the math-gifted group, while in the control group it was activated only in the left hemisphere during both tasks. The DLPFC is the executive center of information maintenance and processing with internal representations during working memory, and is believed to support reasoning and novel problem solving (Baker

et al., 1996; Chafee and Goldman-Rakic, 1998; Goldman-Rakic, 1987, 1995; Lee et al., 2006; Owen et al., 1996; Todd and Marois, 2004). Increased activation in this area is associated with degree of difficulty or acts as a response to a higher cognitive load (Braver et al., 1997; Kroger et al., 2002).

Thus, the greater activation of prefrontal areas observed in the math-gifted group may represent a cognitive advantage, greater ease of processing information, creation of a strategy, or planning (Lazeron et al., 2000; Owen et al., 1996; Wagner et al., 2006).

Fluid reasoning

To solve the RAPM task, subjects need logical reasoning and spatial working memory, because the task requires both greater symbolic and spatial relations to be analyzed (Carpenter et al., 1990). Therefore, activation is associated with both the left and the right frontoparietal cortices and with some left hemispheric dominance. Indeed, the neural network underlying performance in RAPM overlaps substantially with symbolic (non-spatial) working memory networks during analytical reasoning. Therefore, the RAPM task required figural analysis (visuospatial) abilities. The most comprehensive study of the matrix reasoning test (Raven, 1965) reports right frontal hemispheric activations for matrix reasoning during figural problem solving (visuospatial reasoning) (Prabhakaran et al., 1997). Logical reasoning needs the language system to perform the task, and this is associated with left frontal regions (Dehaene et al., 2003, 1999; Kroger et al., 2002).

In the present study, the control group had a bilateral activation pattern, with fewer areas activated than the math-gifted group; they also had less significant clusters in the right parietal cortex. During this task, the math-gifted group showed bilateral activations in both the frontal and parietal cortices, as observed elsewhere (Lee et al., 2006).

Strong activation of the DLPFC bilaterally (mainly the left DLPFC during difficult trials) and the left RLPFC in the math-gifted group may be important to perform the task efficiently. Some authors suggest that,

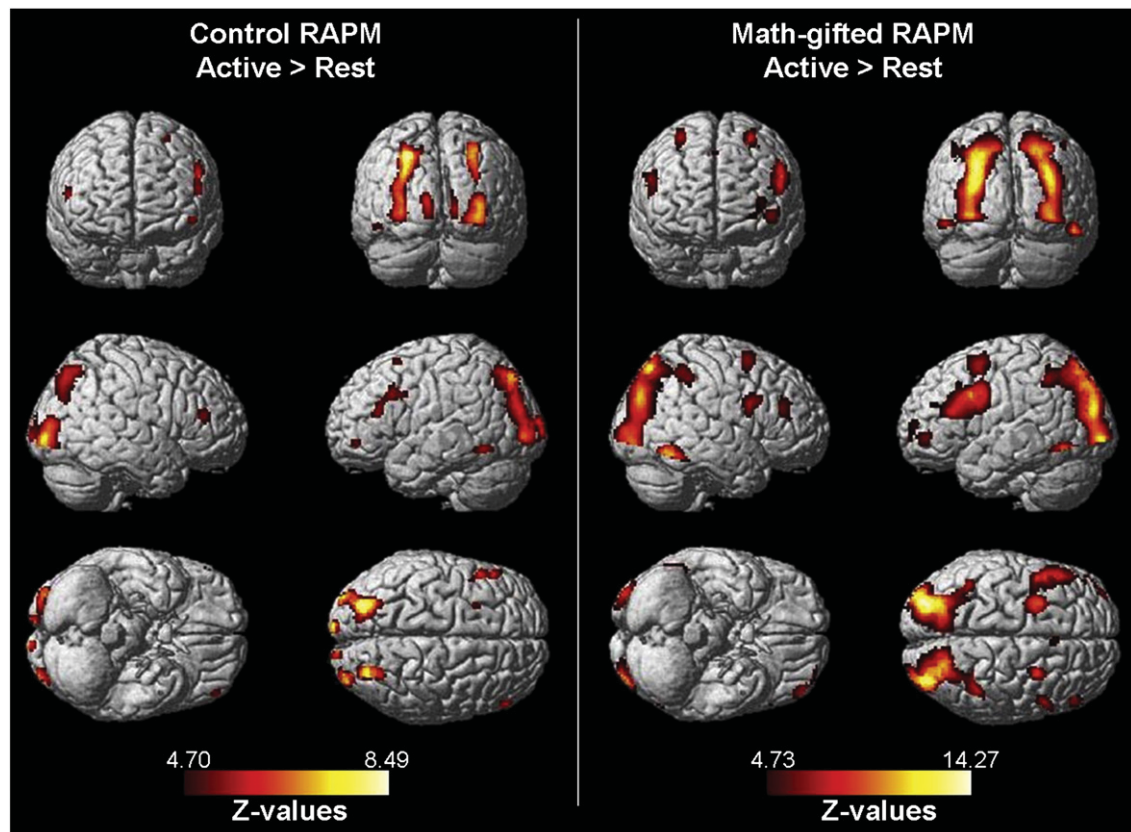


Fig. 4. First-level analyses in math-gifted and control groups during the RAPM task. Clusters showing significant activations are color-coded for each group. Significant clusters are superimposed on the anatomical render (SPM5). The color bar shows the z-score for each group. More activation and bilateralism were observed in the frontal, prefrontal, and parietal cortices in math-gifted adolescents.

during performance of the RAPM task, the RLPFC turns significantly active when the task demands integration of information about the shape of objects (relational integration) (Christoff et al., 2001; Wendelken et al., 2008).

An important point in our results during the RAPM task was that math-gifted subjects showed strong activation in Broca's area, or the left VLPFC (BA 44). This result is consistent with Dehaene's hypothesis that there is interaction between the symbolic system and the visuospatial and mental

Table 7

Between-group analysis, math-gifted adolescents > control group contrast; between condition analysis math-gifted difficult > easy contrast; and between-group analysis in the difficult condition. Anatomical regions showing significant activation during Raven's Advanced Progressive Matrices, the hemisphere (R, right; L, left); the BA, Brodmann Area, the local maxima coordinates in Talairach space (mm), the Z-score and the cluster size (k). Significant differences in regions of activation between the two groups during RAPM task ($t > 3.45$). All regions significant at cluster-level P corrected < 0.05 and voxel-level P uncorrected < 0.001 ($k > 10$), unless marked otherwise.

Raven's Advanced Progressive Matrices					
Region of significant activation	Local maxima				
	Side	BAs	(x, y, z) mm	Z-score	k
<i>Math-gifted > Control</i>					
Postcentral gyrus	R	2	(49, -27, 47)	4.33	220
Inferior parietal lobule	R	40	(65, -27, 38)	3.71	220
<i>Math-gifted (Difficult > Easy)</i>					
Middle occipital gyrus	L**	18	(-22, -103, 7)	5.11	431
	R	18	(12, -95, 10)	4.31	157
Cuneus	L**	19	(-22, -95, 25)	3.97	431
	R	18	(20, -100, 14)	3.62	157
Inferior parietal lobule	R**	40	(44, -38, 52)	3.84	175
Anterior cingulate gyrus	R**	32	(12, 30, 23)	3.63	132
DLPFC; middle frontal gyrus	L**	9	(-49, 6, 35)	4.14	132
Premotor cortex; medial frontal gyrus	R**	6	(0, 16, 47)	3.85	133
<i>Difficult (Math-gifted > Control)</i>					
Inferior parietal lobule	R	40	(65, -27, 40)	3.92	242
Postcentral gyrus	R	2	(55, -27, 44)	4.00	242
Premotor cortex	R*	6	(26, -3, 44)	3.97	217

* Cluster p corrected < 0.01 .

** Cluster p corrected < 0.001 .

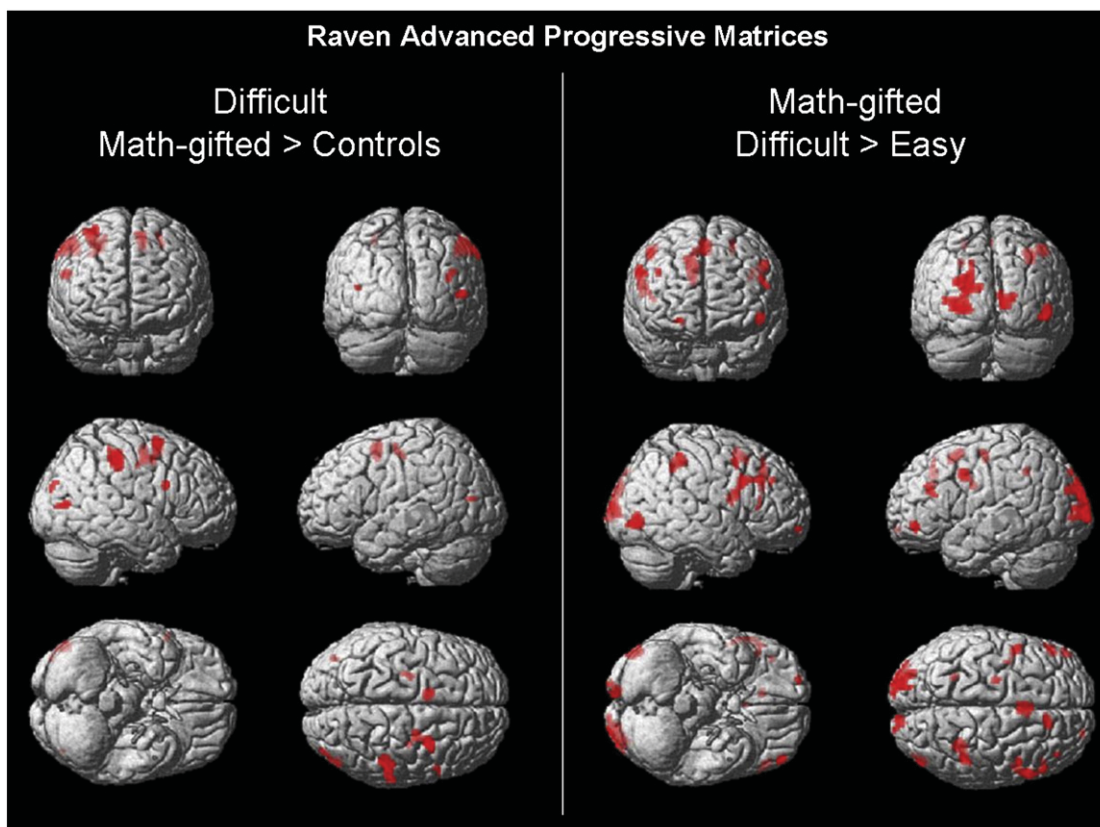


Fig. 5. Left. Random-effects analyses between groups when performing difficult tasks of RAPM; Right. Random-effects analyses between “easy” and “difficult” conditions. Only the math-gifted group showed significant differences.

imagery systems (Dehaene et al., 2003, 1999). Broca’s area has been implicated in deduction problems (Dehaene et al., 1999; Kroger et al., 2002). Another interpretation was proposed by Kroger et al. (2002), who suggested that the neural substrates of logical reasoning and mathematical thinking are not the same, and that high level cognition does not depend on a single global system. Thus, logical reasoning would go beyond linguistic processing to the manipulation of nonlinguistic representations. We found areas that overlap with logical reasoning and spatial working memory.

The math-gifted group showed activation in BA 6 during both tasks. The control group only showed activation in this area during the TOL task. Within the context of this study, the left lateral BA 6 cortex supports processing related to the complexity of the problem. These activations in BA 6 may suggest that the math-gifted group had greater high-level cognitive abilities such as visuospatial and attention processes. Activations in BA 6 have been associated with saccadic eye movements, attention, and visuospatial manipulation (Brown et al., 2004; Courtney et al., 1998; Curtis and D’Esposito, 2003; Curtis et al., 2004; Smith and Jonides, 1999).

One of the most relevant findings of our study is that differences between groups appear only when performing the difficult RAPM trials. No differences were observed between the groups in the neural pattern of activation during the easy trials; in fact, in the control group, no differences between the levels of complexity were observed. The math-gifted group showed more significantly activated regions when the complexity level of the task increased, as if they were using more resources only when necessary.

Most of the significantly activated regions in the math-gifted group during difficult trials are observed in the right hemisphere, suggesting that high complex reasoning involves both an increase in activation of the right hemisphere and more bilateralism in the pattern of activation of the frontoparietal network. In addition, increased activation in math-gifted

subjects during complex tasks was more evident in frontal regions (BA 9 and BA 6) and the anterior cingulate gyrus (BA 32). This was the pattern observed by Lee et al. (2006). Activation also increased with task complexity in the inferior parietal lobule (BA 40) in math-gifted subjects and was significantly different between groups during difficult tasks, suggesting that the parietal cortex, especially on the right hemisphere, may play a crucial role in complex reasoning processes (Dehaene et al., 2003; Lee et al., 2006).

When math-gifted subjects performed difficult trials, higher activation was observed in the anterior cingulate gyrus (BA 32). This finding agrees with those of Gray et al. (2003), who showed that activation of frontal lobes and the anterior cingulate correlate with fluid reasoning (Gray et al., 2003) and also with the results of O’Boyle et al. (2005), who showed that increased activation of the anterior cingulate gyrus was a sign of high functional development of the math-gifted brain (O’Boyle et al., 2005). Other studies have suggested a role for the anterior cingulate when the task becomes more difficult, and this area serves as an on-line regulator of cognitive resource allocation policies (O’Boyle et al., 2005).

Number of slides completed and total display time were significantly lower in easy than in difficult tasks, and this may have affected the analysis of group comparisons within easy or difficult trials. However, both groups showed a similar gap between the number of easy and difficult slides completed and total display time, thus ruling out any group bias due to these differences.

Increased brain activity in the frontal cortex, cingulate gyrus, and parietal regions seems to be associated with higher performance in fluid reasoning and working memory. The largest activations correspond to the increase in task complexity and to high working memory load, both of which confer an advantage to math-gifted adolescents in complex problem solving.

During the RAPM task, activations in the frontoparietal network in both groups could be related to fluid reasoning and working memory. The

greater activations of the math-gifted group, especially during difficult trials, may give this group greater ability to solve problems that need relational reasoning with symbolic and spatial information.

There are several limitations in our study. The first one concerns the cognitive characterization of our two groups. Selection of math-gifted subjects was made using only their performance in the ESTALMAT test, which is specific for detecting math abilities. FSIQ was estimated to rule out atypical cognitive functioning or mental retardation, together with the overall functioning assessment made by the child psychiatrist and child psychologist. A more thorough cognitive assessment could have revealed whether other cognitive differences than mathematical reasoning and problem solving, exist between the two groups. However, our study is focused on brain mapping of subjects with precocious mathematical abilities, rather than investigating cognitive performance or overall intelligence. Thus, although math-gifted subjects showed other cognitive skills in addition to math, the only criteria used for selection was math-giftedness, which was assessed with a highly specific test. To rule out a statistical effect of IQ on the activation pattern observed, we performed a correlation and covariate analysis, which suggest that the confounding effect was minimal (see [Methods](#) and [Supplementary Results](#)). Another limitation was that the paradigm used was not specific for mathematical thinking; such a paradigm would have yielded more information about the brain regions involved when the subject was engaged in a mathematical task. A paradigm assessing global mathematical abilities could have proven useful, by increasing group differences and minimizing the confounding effect of multiple cognitive abilities in the math-gifted subjects. However, no such specific paradigm has been reported in the literature; therefore, we chose two tasks which we believe provide an adequate context in which to analyze mathematical thinking. Finally, our findings about the brain response to increased task complexity only apply to fluid reasoning. Thus, the effect of complexity level on executive function should be analyzed in a specific study.

Conclusions

In summary, the differences between subjects with or without mathematical ability in complex cognitive processes such as fluid reasoning, executive functioning, and visuospatial working memory seem to be mediated by the neural activity of the bilateral frontoparietal network. In the math-gifted group, we observed greater bilateralism of activation in the frontoparietal network (especially the posterior parietal cortex, intraparietal sulcus, and DLPFC), which is probably associated with the higher capacity of math-gifted subjects to solve complex visuospatial and analytical tasks demanding logical thinking. During easy tasks, activation patterns were similar in both groups, whereas major differences between groups appeared only during difficult tasks, mainly in the frontal cortex and inferior parietal lobule. Functional specialization of math-giftedness has been described as a combination of greater recruitment of right hemisphere regions and more bilateralism (O'Boyle et al., 2005; Prescott et al., 2010). In contrast to an explanation based on neural efficiency, our study further supports this hypothesis of stronger recruitment of math-gifted children. Therefore, math-gifted subjects are qualitatively different in terms of the degree and location of activated brain regions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.03.063.

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Appendix Chapter 3

In this appendix, we intend to demonstrate that IQ scores have low effect on brain activations during task performance. We present, firstly a correlation analysis between the parametric maps and the IQ of each subject for the whole sample; and secondly, we present the results of the one-sample t-test adding the IQ as a covariate for each group and for each task.

Figure 3.A1. Results of an SPM Analysis of correlation between values of the effect size of activation vs baseline during the TOL task and estimated FSIQ. Clusters show brain areas showing significant ($p < 0.001$, uncorrected) correlations. All subjects ($n=27$) were included in the analysis.

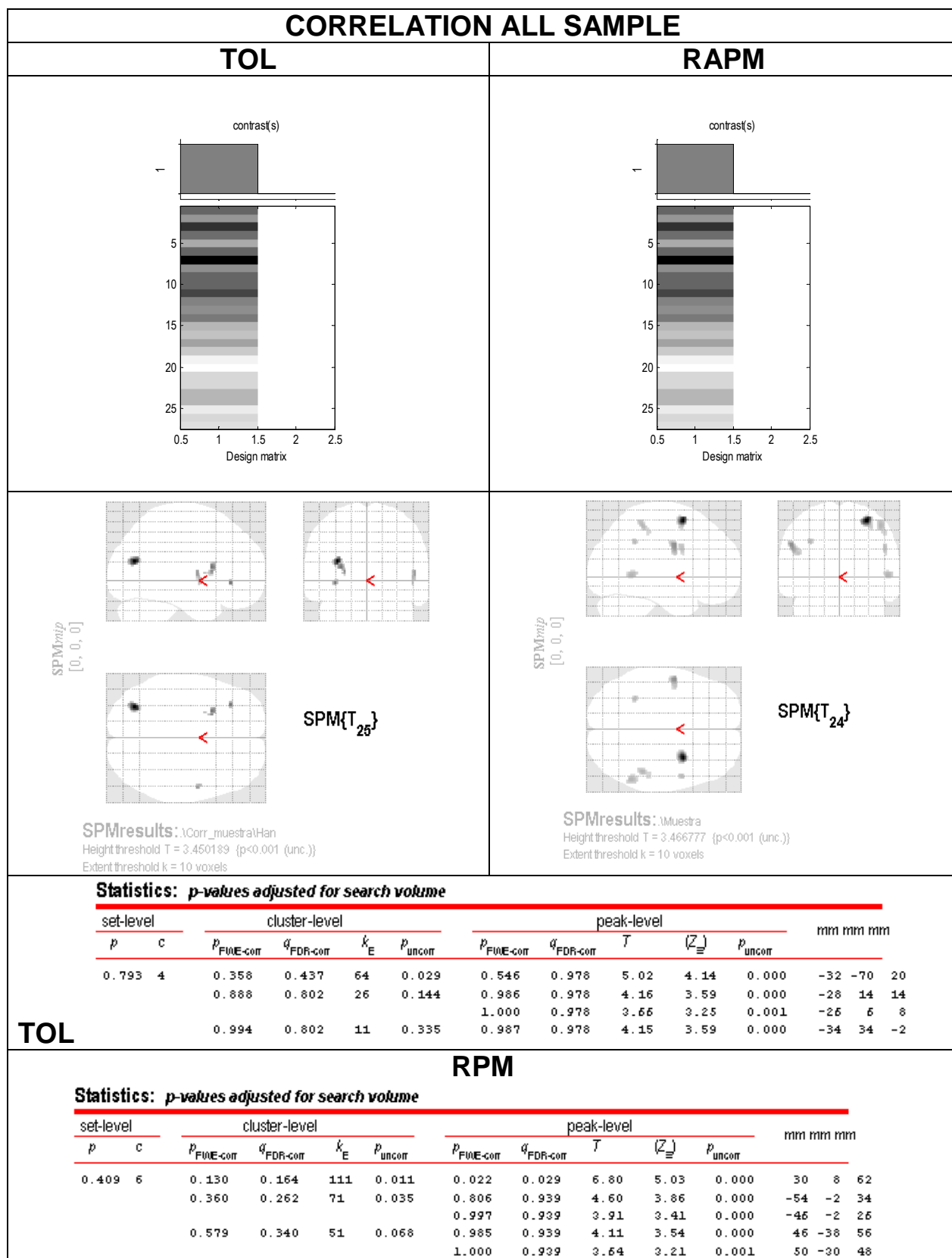
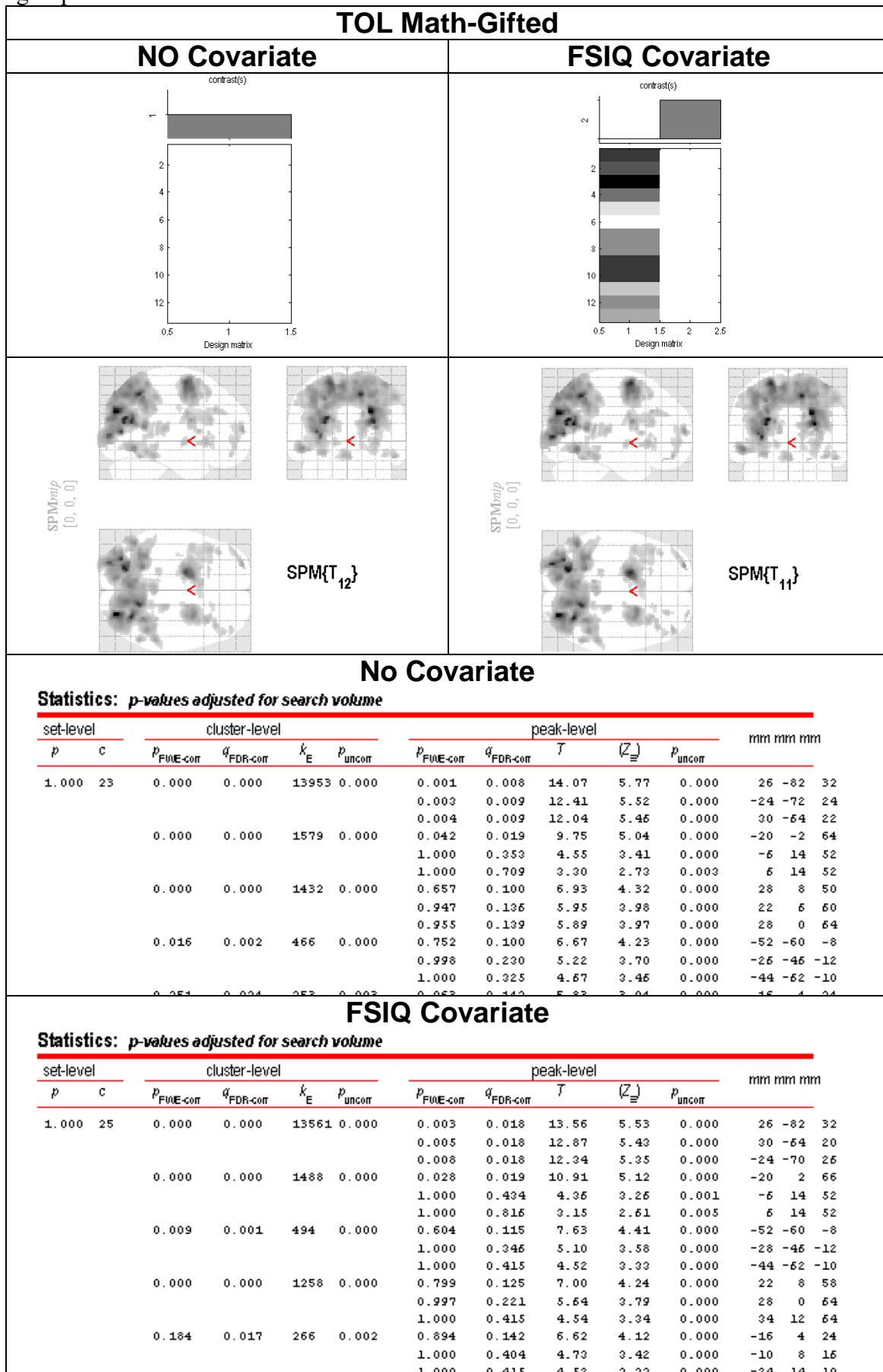
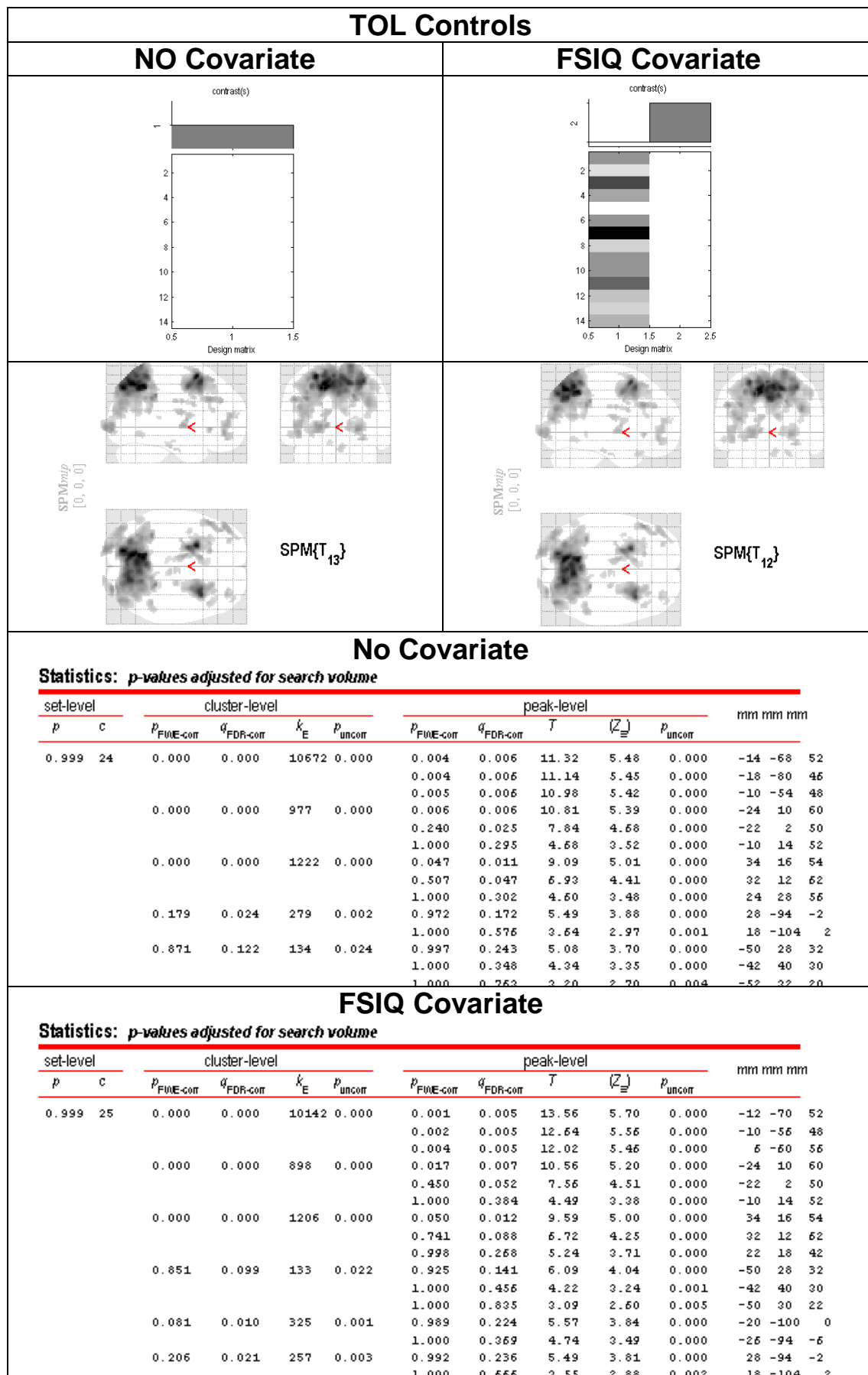
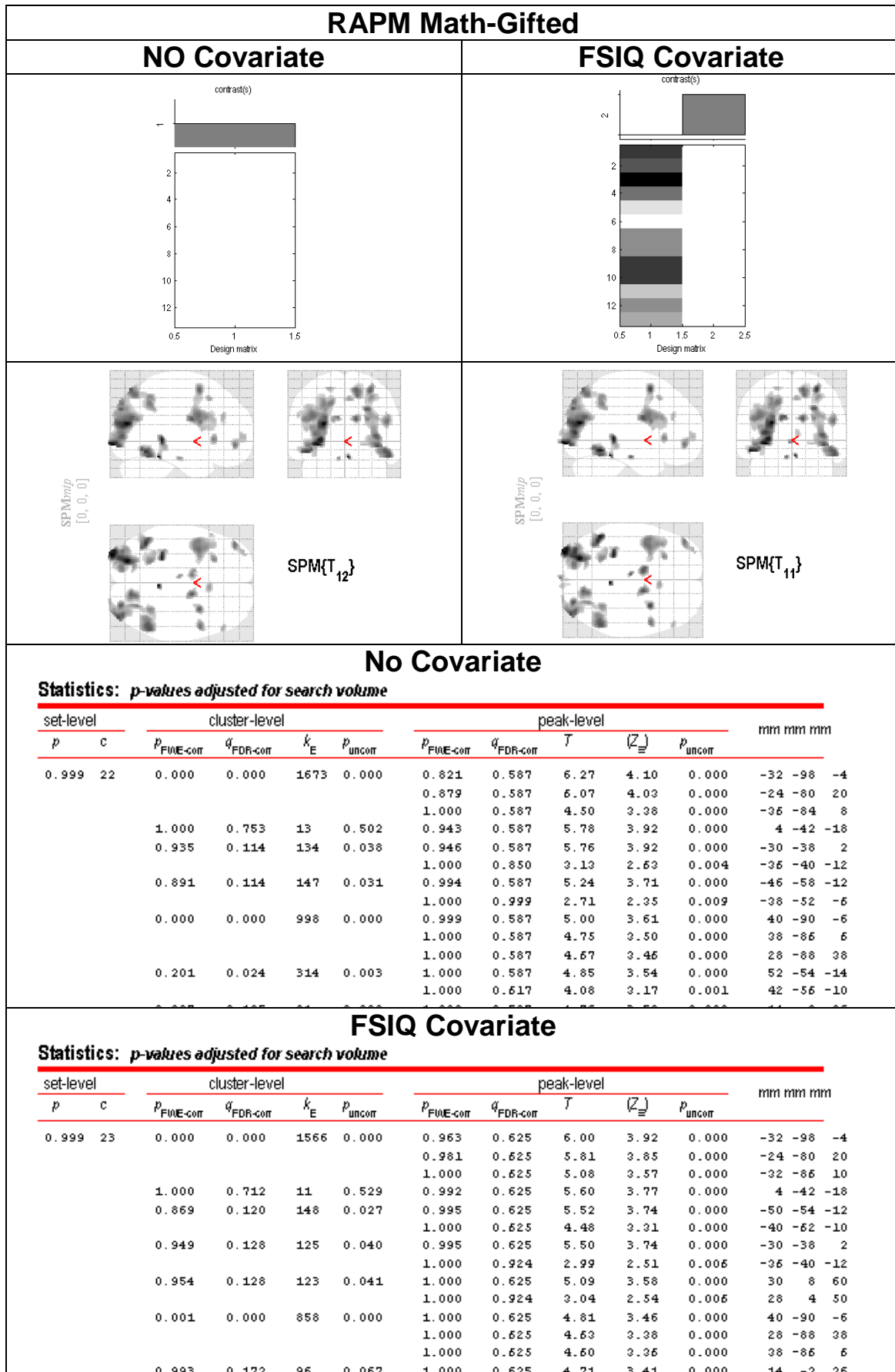
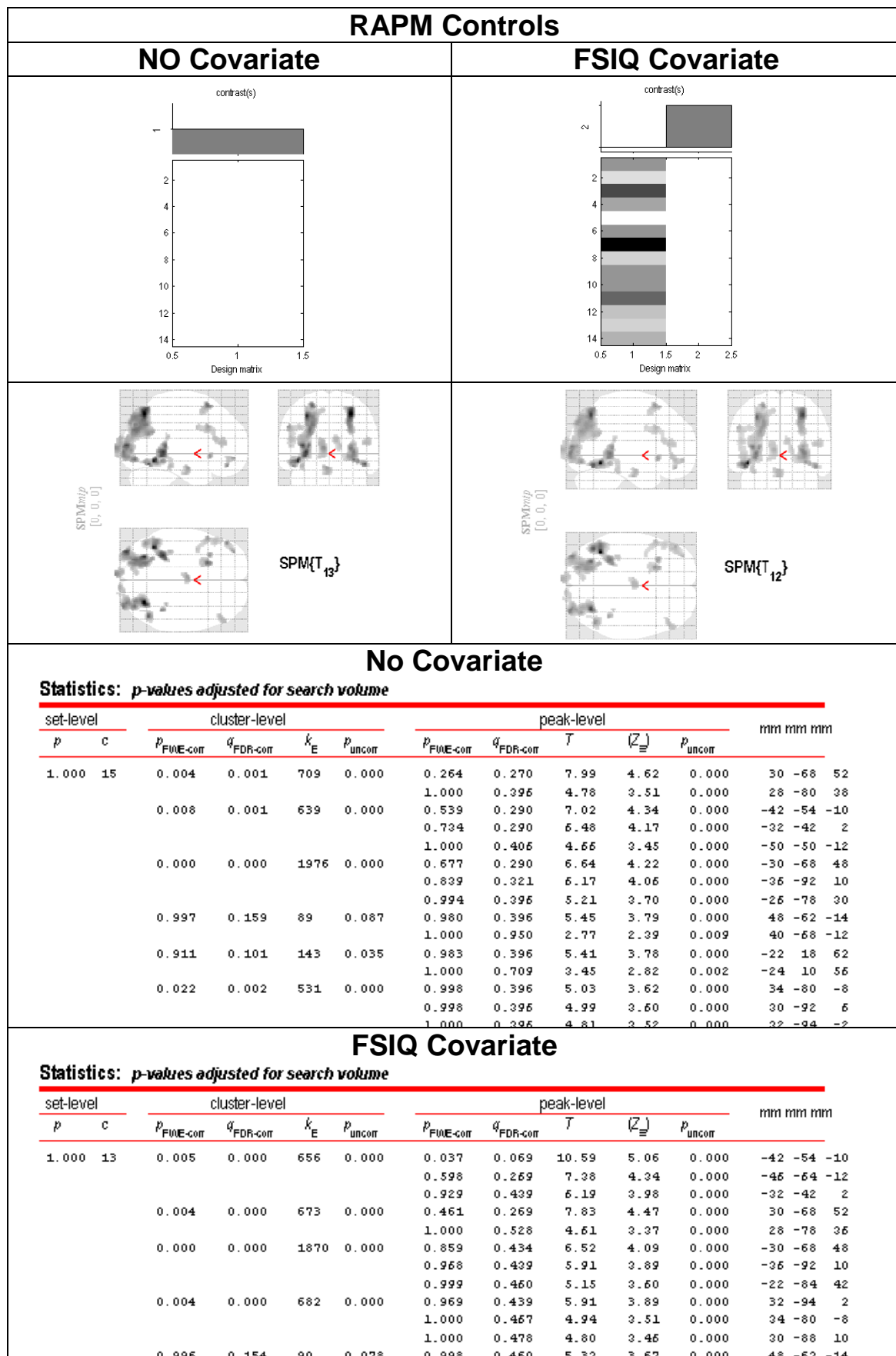


Figure 3.A2. Results of SPM Analysis of a one-sample t-test of mean values of the effect size of activation vs baseline for TOL and RPM tasks in both groups. Left and right column: model with or without covariate. This map represents the areas with significant ($p < 0.01$, uncorrected) activation response during the task, within each group.









Chapter 4. White Matter Microstructure Correlates of Mathematical Giftedness and Intelligent Quotient

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White Matter Microstructure Correlates of Mathematical Giftedness and Intelligence Quotient

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Abstract: Recent functional neuroimaging studies have shown differences in brain activation between mathematically gifted adolescents and controls. The aim of this study was to investigate the relationship between mathematical giftedness, intelligent quotient (IQ), and the microstructure of white matter tracts in a sample composed of math-gifted adolescents and aged-matched controls. Math-gifted subjects were selected through a national program based on detecting enhanced visuospatial abilities and creative thinking. We used diffusion tensor imaging to assess white matter microstructure in neuroanatomical connectivity. The processing included voxel-wise and region of interest-based analyses of the fractional anisotropy (FA), a parameter which is purportedly related to white matter microstructure. In a whole-sample analysis, IQ showed a significant positive correlation with FA, mainly in the corpus callosum, supporting the idea that efficient information transfer between hemispheres is crucial for higher intellectual capabilities. In addition, math-gifted adolescents showed increased FA (adjusted for IQ) in white matter tracts connecting frontal lobes with basal ganglia and parietal regions. The enhanced anatomical connectivity observed in the forceps minor and splenium may underlie the greater fluid reasoning, visuospatial working memory, and creative capabilities of these children. *Hum Brain Mapp* 00:000–000, 2013. © 2013 Wiley Periodicals, Inc.

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Key words: mathematical giftedness; adolescents; DTI; fractional anisotropy; intelligence; IQ; corpus callosum; fronto-parietal; white matter

INTRODUCTION

The neural basis of intelligence and the processes that underlie giftedness are areas of increasing interest. Gifted children are precocious in their intellectual development and show intelligence quotient (IQ) values that are higher than 2 standard deviations above the population mean. However, enhanced abilities in a domain-specific area are not necessarily dependent on IQ, but rather a reflection of other neurobiological characteristics [Kalbfleisch, 2004], such as cortical dynamics of maturation, genetic factors, or brain volume. Defining giftedness only by higher IQ could lead to confusion in the identification of gifted subjects. Math-gifted subjects perform better in novel problem solving by using innovative selection criteria and are able to perceive complex relations and form concepts faster than nongifted subjects [Jung et al., 2010; O'Boyle et al., 2005]. In addition, they store and manipulate outcomes more efficiently and creatively. The creative aspects of intelligence are accompanied by enhanced cognitive processes such as fluid reasoning and working memory [Geake and Hansen, 2005]. Math-gifted subjects show higher capabilities in fluid reasoning, working memory, and mental imagery [Desco et al., 2011; Lee et al., 2006; O'Boyle et al., 2005].

Previous neuroimaging studies of math-giftedness suggested that the organization of a math-gifted brain could be different from that of a nongifted brain. These studies reported functional characteristics of math-gifted adolescents performing visuospatial and fluid reasoning tasks [Desco et al., 2011; Lee et al., 2006; O'Boyle et al., 2005]. The combination of a special form of bilateralism in a fronto-parietal network and enhanced functioning of the right hemisphere seems to be the neurobiological substrate of math-giftedness [Benbow, 1986; Benbow and Lubinski, 1993; Geschwind and Galaburda, 1984; O'Boyle et al., 1991, 1995]. These characteristics involve heightened connectivity between the left and right hemispheres [Singh and O'Boyle, 2004], as well as enhanced intrahemispheric connectivity between the frontal and parietal cortices [Desco et al., 2011]. To our knowledge, no studies on white matter microstructure have confirmed heightened connectivity in math-gifted subjects.

In this study, we investigate the white matter microstructure underlying math giftedness. We used diffusion tensor imaging (DTI) to provide a framework for analysis and quantification of the diffusion properties of white matter. Specifically, fractional anisotropy (FA) makes it possible to assess myelin and axonal microstructure in white matter [Basser, 1997; Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996]. Increased FA may depend on increased fiber density, increased myelination of fiber tracts, higher directionally coherent organization of fibers within voxels

[Beaulieu, 2002], or increased axonal diameter [Mori and Zhang, 2006]. Some studies have shown a relationship between FA and intelligence [Schmithorst and Holland, 2007; Schmithorst et al., 2005; Yu et al., 2008], arithmetic and mathematical calculation scores [Tsang et al., 2009; van Eimeren et al., 2010], working memory scores [Nagy et al., 2004], and visuospatial processing [Klingberg, 2006; Mabbott et al., 2006; Wolbers et al., 2006] in white matter fronto-parietal areas. These correlations were thought to reflect a positive relationship between white matter organization and higher intelligence, thus supporting the Parieto-Frontal Integration Theory [Jung and Haier, 2007].

The objective of our study was to investigate the relationship between math-giftedness/IQ and white matter FA in a sample composed of math-gifted adolescents and age-matched controls. We hypothesized that math-gifted subjects, independently of their IQ, would have bilateral increased FA in the intrahemispheric tracts, particularly in the fronto-parietal regions, and in the interhemispheric commissure tracts, especially in the corpus callosum.

METHODS

Subjects

The sample recruited for the study included a total of 36 adolescents aged between 11.8 and 15 years who were divided into two groups: math-gifted subjects and age-matched controls. The inclusion criteria for both groups were as follows: age 11–15 years, right-handedness, Spanish as mother tongue, and at least 5 years' schooling in the Spanish education system. Handedness was determined in all subjects using item# 5A of the Neurological Evaluation Scale [Buchanan and Heinrichs, 1989].

The exclusion criteria for both groups were as follows: medical, neurological, or psychiatric illness; history of head injury with loss of consciousness; presence of metallic implants, body tattoos, or orthodontic appliances; mental retardation; pervasive developmental disorders; and pregnancy or breast-feeding.

Math-gifted subjects

The math-gifted group comprised 13 adolescents (5 girls) aged 12–14 years (mean 13.8 years, SD = 0.6) with a mean of 7.8 years of formal education (SD = 0.7). The students were enrolled in the Stimulus of Mathematical Talent Program (ESTALMAT (<http://www.uam.es/proyectosinv/estalmat/>), "Programa de Estimulo del Talento Matemático") of the Spanish Royal Academy of Mathematical, Physical, and Natural Sciences in Madrid. To enter the ESTALMAT program, children who are particularly

◆ White Matter Microstructure ◆

good at math and willing to participate are proposed by teachers and parents. These subjects undergo a screening process consisting of a personal interview and math-related tests. If they pass this preliminary assessment, they undergo a second examination based on a variety of tests that include logical thinking, geometrical representations, and abstract and deductive reasoning. The ESTALMAT tests are intended to select only a few subjects (typically 20 out of 300 in the Madrid region per year). The objective of the tests is to detect the six complex mathematical abilities proposed by K. Kiesswetter [Heller et al., 2000], as follows: (1) organizing materials; (2) recognizing patterns or rules; (3) changing the representation of the problem and recognizing patterns and rules in this new area; (4) comprehending and working with highly complex structures; (5) reversing and inverting processes; and (6) finding related problems. These six abilities could be categorized as cognitive, motivational, and creative.

Test answers were examined by mathematicians considering not only whether the answers were correct, but also the argumentation followed to achieve the solution. Each exam has six different tests in which visuospatial thinking, intuition, creativity, abstraction, manipulation, and capabilities of thought management are assessed. The tests chosen are as original as possible; subjects that have training would not have a clear advantage over the others. In comparison with other standardized measures such as SAT-Math (Scholastic Assessment Test, Mathematics Section), ESTALMAT emphasizes problem solving by creative thinking, rather than using concepts and previous expertise gained at school.

Controls

The control group included 23 adolescents (4 females) aged 12–15 years (mean 13.4 years, $SD = 0.8$). Controls were recruited to match math-gifted subjects for age and academic level, but not explicitly for IQ. The study was presented first in the schools attended by math-gifted subjects, and the selection process of control subjects involved an initial interview to confirm suitability (i.e., age, sex, parental consent, availability, and basic exclusion criteria).

Cognitive Assessment

Intellectual functioning was estimated using the Vocabulary, Information, and Block Design subtests from the Spanish version of the Wechsler Intelligence Scale for Children—Revised. IQ was estimated from these three subtests following [Ringe et al., 2002; Silverstein, 1985] and is reported to show good correspondence with full-scale IQ (FSIQ) [Satler, 2001]. The cognitive assessment was performed by a child neuropsychologist and a child psychiatrist, who also analyzed the subjects' school records.

The study was approved by the Hospital Ethics and Clinical Research Boards. Written informed consent was

obtained from both subjects and parents before the study was performed.

Magnetic Resonance Imaging Acquisition Protocols

Data were acquired with a Philips Intera 1.5 T MRI scanner (Philips Medical Systems, Best, The Netherlands). The protocol included a high-resolution structural image (T_1 -weighted gradient-echo; repetition time (TR) = 25 ms; echo time (TE) = 9.2 ms; matrix size = $256 \times 256 \times 175$; flip angle = 30° ; slice thickness = 1 mm; voxel size $1 \times 1 \times 1 \text{ mm}^3$ 3D) and a DTI study.

DTI data were acquired using a single-shot spin echo-planar imaging sequence with the following scanning parameters: imaging plane, axial; phase encoding direction, A–P; TE = 68 ms, TR = 11,886 ms; flip angle = 90° ; echo-planar imaging (EPI) factor = 77; number of slices = 60; interslice gap = 0 mm; voxel size = $2.0 \times 2.0 \times 2.0 \text{ mm}^3$; and acquisition matrix 128×128 . A single nondiffusion-weighted image and 16 diffusion weighted images were acquired. The diffusion weighted images were obtained for a b -value = 0 and 800 s/mm^2 over 16 noncollinear directions following an icosahedral scheme.

Data Preprocessing and Analysis

Diffusion-weighted studies were processed using the software package FSL 4.1 (FMRIB Software Library, FMRIB, Oxford, UK) [Smith et al., 2004]. Eddy-current and head motion artifacts were corrected using the eddy correct routine implemented in FSL. In this step, all diffusion volumes were registered to the T_2 - b_0 image using an affine transformation. The corresponding diffusion gradient vectors were properly reoriented using the resulting transformations.

Brain masks were obtained from the b_0 image using Brain Extraction Tool [Smith, 2002], and FMRIB's diffusion toolbox [Behrens et al., 2003] was used to fit the tensors and to compute the FA maps.

On the FA maps, we performed both voxel-wise and region of interest (ROI) analyses to study IQ effects on white matter microstructure. After controlling for IQ, we studied the differences between the math-gifted group and the controls.

Voxel-Based Analysis

Voxel-wise statistical analysis of the FA data was performed using FSL tools according to the following workflow. All subjects' FA maps were nonlinearly registered to a target image identified automatically as the most "representative" subject in the study. The most representative FA image was chosen by performing all possible pairwise registrations (linear and nonlinear) between subjects. From this, the subject's image with the minimum mean

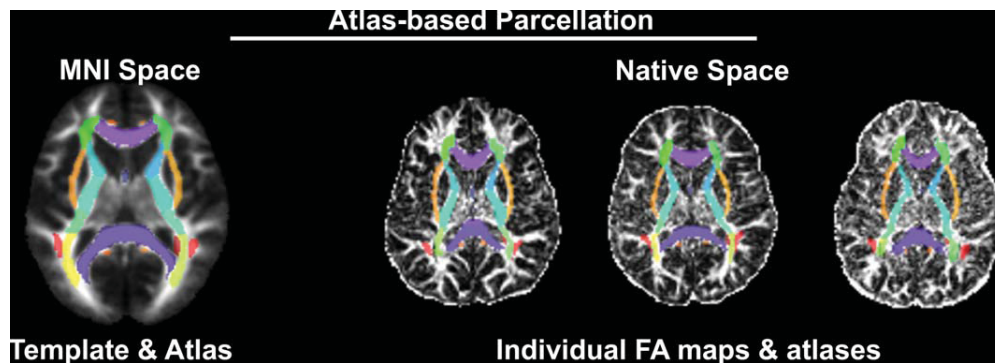


Figure 1.

Atlas-based parcellation method. On the left side, anatomically defined fibers in the ICBM-DTI-81 white matter labels atlas in MNI space. FA maps of each subject were registered to the template in MNI space. The transformation matrices obtained were inverted and applied to the atlas. On the right side, the resulting atlas transformation in the native space of each subject.

deformation necessary to nonlinearly align it to the other subjects was used as the reference. Normalization into the Montreal Neurological Institute (MNI) standard space was performed using the FMRIB Nonlinear Image Registration Tool. All normalized FA images were averaged to obtain a study-specific “Mean FA” template. FA maps were smoothed using a 6-mm Full-Width at Half Maximum (FWHM) Gaussian filter. We used an explicit mask that includes the major white matter pathways but excludes peripheral tracts showing significant intersubject variability and/or partial volume effects with gray matter or cerebrospinal fluid tissues. Only voxels with FA > 0.3 were selected for further analysis.

Finally, a general linear model was applied using non-parametric permutation inference [Nichols and Holmes, 2002]. A statistical analysis using ANCOVA model was carried out on the FA maps to detect possible significant effects of the factor “Math-giftedness” (statistical threshold of $P < 0.05$, corrected for multiple comparisons) and the continuous covariate “IQ.” P -values were corrected using the FDR tool available in the FSL package (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDR>).

Before performing these analyses, we also checked possible gender and age effects on the FA, together with potential interactions with the factor “Math-giftedness” and the covariate “IQ.”

Atlas-Based Segmentation of White Matter Tracts

We extracted the mean FA values of the tracts using an ROI analysis in order to generate an individualized atlas for each subject in native space. To parcel the individual FA maps into different tracts, we used the ICBM-DTI-81 white matter labels atlas, which is one of the standard atlases of FSL [Mori et al., 2008; Wakana et al., 2004]. The JHU-FA template was rigidly registered to the mean FA to

move the white matter labels into the study-specific template space. These labels were then warped into individual spaces by applying the inverted spatial transformation matrices generated by the normalization of the individual FA maps to obtain individual white matter tract parcels. Individualized ROIs were also used to anatomically label the results obtained in the voxel-wise analysis step (Fig. 1).

White matter structures included in the atlas-based segmentation analysis (for each hemisphere) were: Genu, Body, and Splenium of corpus callosum and the whole Corpus callosum; Anterior limb of internal capsule; Posterior limb of internal capsule; Retrolenticular part of internal capsule; External capsule; Anterior corona radiata; Superior corona radiata; Posterior corona radiata; Posterior thalamic radiation; Sagittal striatum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus); Cingulum (cingulate gyrus); Superior longitudinal fasciculus; Superior fronto-occipital fasciculus and Uncinate fasciculus.

Mean FA measurements obtained for each ROI were analyzed with SPSS v13 using the Univariate General Linear Model with “Math-giftedness” as a fixed factor, and “IQ” as a between-subject continuous covariate if an effect on FA was recorded. All the results obtained in the ROI analysis underwent a Bonferroni correction for multiple comparisons ($P < 0.05$).

RESULTS

The results of the cognitive assessment showed significant differences in IQ. The math-gifted group had a mean estimated FSIQ of 130.7 (SD = 10.7; range, 112–149). Controls were recruited randomly from the same schools as the math-gifted adolescents and had a mean estimated FSIQ of 105.5 (SD = 15.7), with a wider IQ range than the math-gifted subjects (88–140). There are significant between-group differences in both VIQ and PIQ scores

◆ White Matter Microstructure ◆

TABLE I. Mean and standard deviation (SD) of demographic data for each group

	Controls (n = 23)		Math-gifted (n = 13)		Pa
	Mean	SD	Mean	SD	
Age (years)	13.42	0.86	13.75	0.57	
Age (months)	160.91	10.31	165.01	7	
Gender (male\female)	19\4		8\5		
Handedness (right\left\mixed)	23\0\0		13\0\0		
Estimated full-scale IQ	105.48	15.71	130.77	10.68	<0.001
Verbal IQ	106.83	16.67	125.08	12.07	<0.001
Performance IQ	99.83	23.1	128.85	12.14	<0.001

^a Student's *t* test of differences between groups.

($P < 0.001$). In both groups, there are no significant differences between Verbal (VIQ) and Performance IQ (PIQ) scores, thus suggesting a balanced intellectual profile (see Table I). Years of education and parental socioeconomic status were similar in both groups.

Relationship Between FA and IQ

In the voxel-wise analysis of the whole sample, IQ correlated positively with FA, mainly in the corpus callosum. The atlas-based analysis showed that the effect of IQ correlated with mean FA for the whole corpus callosum (Pearson's $r = 0.48$; $P < 0.003$) and its parts: genu ($r = 0.38$; $P < 0.021$), body ($r = 0.476$; $P < 0.003$), and splenium ($r = 0.46$; $P < 0.005$). These results are plotted in Figure 2.

We also found significant clusters in association tracts (Table II); however, only the fornix ($r = 0.36$; $P < 0.031$) and anterior limb of the left internal capsule ($r = 0.38$; $P < 0.022$) had an IQ effect on mean FA for the whole tract.

Differences in FA Between Math-Gifted Subjects and Controls

In the voxelwise analysis, after adjustment for the effect of IQ, the math-gifted group showed significantly higher FA bilaterally in association tracts, in the anterior and superior corona radiata (including corticospinal tract), and in the genu and the splenium of the corpus callosum, particularly in the forceps minor and major (Table III; Fig. 3). Most of the association tracts with higher bilateral FA connect frontal lobes with basal ganglia (anterior and posterior limbs of the internal capsules, right external capsule, and thalamic radiations) and temporo-parietal regions (uncinate, superior, and inferior longitudinal fasciculi) adjacent to the inferior parietal lobule. Controls did not show any region with significantly higher FA than math-gifted group. Figure 4 shows the between-group differences in the atlas-based parcellation analysis in native space,

plotted with statistical “*F*-values.” No significant group \times IQ interaction was observed in the tracts analyzed.

To ensure that IQ effects are not confounded with those of the construct of “mathematical giftedness,” we also prepared an IQ-matched subsample with high-IQ controls (IQ = 108–137, $n = 9$) and math-gifted subjects (IQ = 112–149, $n = 13$). No significant between-group difference in IQ scores was found. In this subsample, the “Gifted” group still showed significantly higher FA in the same tracts as in the analysis reported above, and in the left uncinate and right posterior corona radiata.

To verify potential gender- and age-related effects on FA, we used an ANCOVA model including “Age” as a continuous variable and “Gender” as a factor. The introduction of “Age” as a continuous covariate led to a non-significant effect in the ANCOVA model, and the main effect of “Group” did not change. In the same way, the introduction of the factor “Gender” in the ANCOVA model (together with the interactions Gender \times IQ and Gender \times Group) in both voxelwise and ROI analyses did not reveal a significant effect of Gender or the Group \times Gender interaction in any tract. As an additional verification, we repeated the whole analysis for the male subsample only, and the results remained unchanged. Furthermore, after checking potential interactions such as “Group \times Gender” and “IQ \times Gender,” we did not observe any significant effect.

Consequently, because age- and gender-related effects were not significant and did not affect the overall results, we decided to exclude them for the sake of model parsimony, which is an important consideration when sample size is reduced.

DISCUSSION

We investigated the association between math-giftedness/IQ and the microstructure of white matter tracts in a sample composed of math-gifted adolescents and age-matched controls. To our knowledge, this study is the first to assess adolescents with math-giftedness using DTI.

We observed that IQ score correlates positively with FA of the corpus callosum. Math-gifted subjects showed increased FA independently of their IQ in fronto-parietal and fronto-striatal association tracts and in some regions of the corpus callosum.

As for the neurobiological substrate of math-giftedness, the organization of a math-gifted brain can involve functional bilateralism and enhanced fronto-parietal connectivity [Singh and O'Boyle, 2004]. The fronto-parietal network and enhanced interhemispheric connectivity have been associated with high-level intelligence [Gray and Thompson, 2004; Gray et al., 2003; Jung and Haier, 2007], mathematical skills [Tsang et al., 2009; van Eimeren et al., 2010], and creativity [Finke, 1996; Takeuchi et al., 2010]. A previous fMRI study from our group with the same math-gifted sample supported this model and provided new fMRI

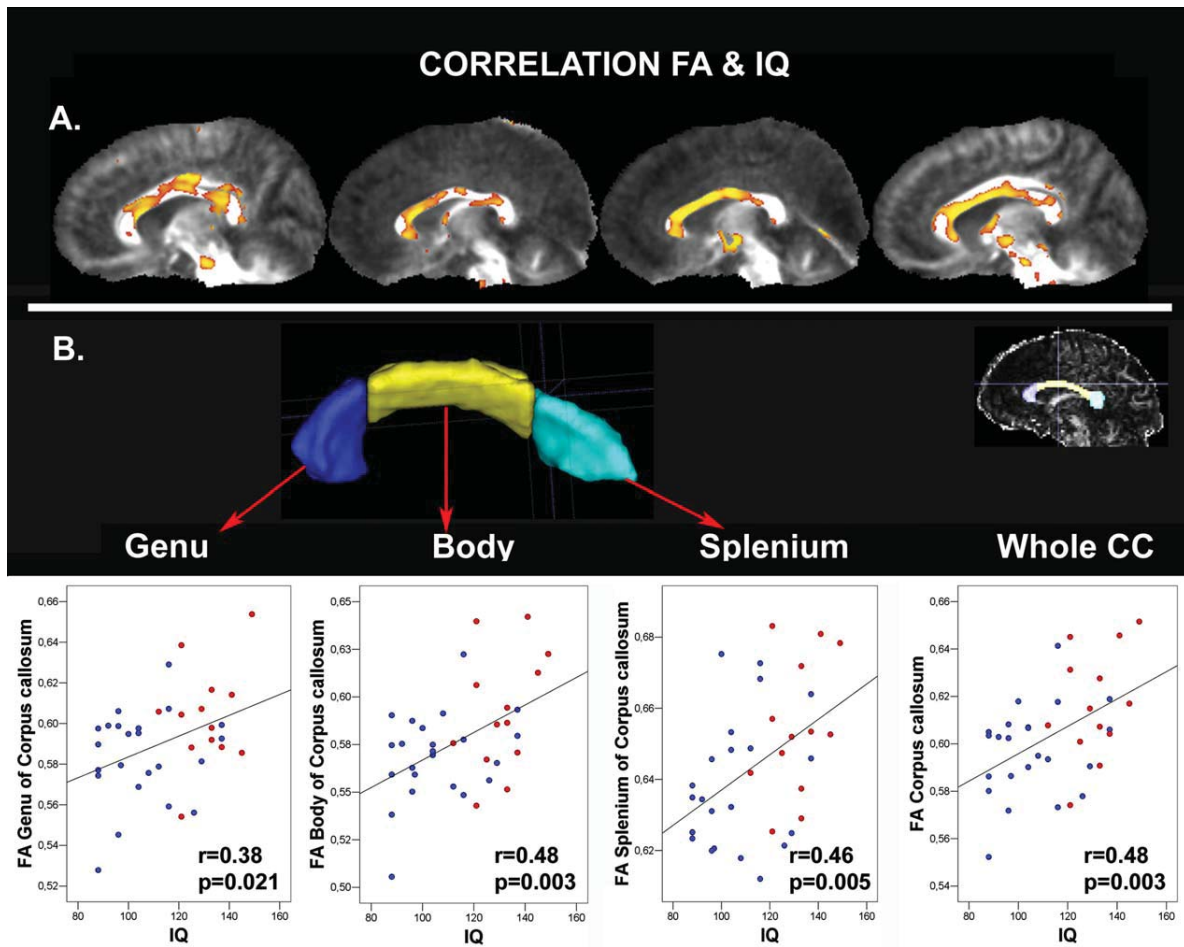


Figure 2.

Correlation between FA and IQ in the voxel-wise analysis. **A:** Correlation between FA and IQ in the corpus callosum and cingulum in the voxel-wise analysis ($P = 0.05$ uncorrected). Significant clusters were overlaid on the mean FA image from all

subjects. **B:** Correlation scatter-plot from the atlas-based parcellation with FA obtained from each part of the corpus callosum in native space. Math-gifted subjects are represented in the graphs in red color circles; controls in blue.

evidence from executive functioning and two complexity levels of fluid reasoning tasks [Desco et al., 2011].

Interhemispheric White Matter Microstructure and High-Level Intelligence

We found in the whole sample a positive correlation between IQ and FA in much of the corpus callosum and in some frontal and parietal association tracts. Consistent with our hypothesis, heightened anatomical connectivity in the corpus callosum seems to correlate with higher intelligence. The corpus callosum is the most important structure for communication of information between homologous regions of the cerebral hemispheres [Hofer and Frahm,

2006]. The corpus callosum microstructure is associated with hemisphere dominance in healthy people [Haberling et al., 2011], working memory processing [Fryer et al., 2008], and intelligence [Hutchinson et al., 2009; Yu et al., 2008]. Besides the effect of IQ on the corpus callosum described above, we also observed an additional independent effect of math-giftedness localized in the genu and splenium. The prefrontal cortices are interconnected along the forceps minor and genu, the most anterior part of the corpus callosum. Increased white matter organization in the prefrontal part of the corpus callosum might be related to improved high-level cognitive processes such as fluid reasoning, executive functioning, and working memory [Carpenter et al., 2000; Christoff et al., 2001; Colom et al., 2003; Curtis and D'Esposito, 2003; D'Esposito et al., 1995; Gray

◆ White Matter Microstructure ◆

TABLE II. Anatomical regions showed significant correlation between FA and IQ in the voxel-wise analysis

Voxel-wise Analysis: Correlation FA-IQ						
Anatomical region	Hemisphere	<i>x</i>	<i>y</i>	<i>z</i>	Z-value	Cluster size
Genu of corpus callosum	Left	-2	5	25	3.35	6,603
Body of corpus callosum	Left	-3	5	24	3.1	6,603
Splenium of corpus callosum	Left	0	-36	8	2.13	34
Cingulum	Right	11	-35	30	3.35	1,885
Cingulum (hippocampus)	Right	25	-48	1	3.54	603
	Left	-26	-36	10	2.7	55
Forceps major	Right	7	-44	9	2.08	31
Fornix	Right	1	2	8	2.34	74
Anterior limb of internal capsule	Left	-9	2	5	2.47	336
External capsule (uncinate)	Left	-33	40	-2	3.03	350
Anterior thalamic radiation	Left	-2	-11	-6	3.35	663

The table only reports Z-values >1.90 ($P < 0.05$, uncorrected).

TABLE III. Anatomical regions with significant increased FA in math-gifted subjects compared with controls obtained in the voxel-wise analysis

Voxel-wise analysis: FA math-gifted > controls						
Anatomical region	Hemisphere	Local maxima			Z-value	Cluster size
		<i>x</i>	<i>y</i>	<i>z</i>		
Corticospinal tract	Right	17	-21	70	2.84	9,387
	Left	-23	-21	50	3.29	2,252
Anterior corona radiata (cingulum, fminor)	Right	22	30	27	3.66	9,387
	Left	-17	40	10	2.66	875
Anterior corona radiata (IFOF/Unc)	Left	-23	36	-1	2.94	291
Superior corona radiata	Right	19	-5	40	3.31	9,387
	Left	-25	7	22	3.3	2,252
Posterior corona radiata	Right	26	-31	22	2.49	25
	Left	-27	-32	23	2.69	44
External capsule	Right	29	-8	16	2.61	38
Anterior limb internal capsule	Right	22	16	7	2.96	191
	Left	-23	11	14	2.64	2,252
Posterior limb internal capsule	Right	15	-15	14	3.18	9,387
	Left	-22	-15	17	3.37	2,252
Retrolenticular part of internal capsule	Right	33	-36	14	2.49	30
Anterior thalamic radiation	Right	18	-14	12	3.18	9,387
	Left	-16	-5	8	2.68	2,252
Posterior thalamic radiation	Left	-35	-46	13	2.97	343
Superior longitudinal fasciculus	Right	45	-21	44	2.89	179
	Left	-38	-36	31	3.62	310
Inferior longitudinal fasciculus	Right	35	-70	-3	3.05	85
	Left	-49	-17	-17	2.58	293
Inferior fronto-occipital fasciculus	Right	21	-87	17	3.01	45
Forceps minor	Right	18	48	-2	3.26	9,387
	Left	-16	43	21	3.04	875
Forceps major	Right	19	-85	17	2.4	40
Genu of corpus callosum	Left	-14	37	9	2.4	875
Splenium of corpus callosum	Left	-23	-85	1	2.55	30
Uncinate fasciculus	Left	-25	39	-1	2.79	291

The table only reports Z-values >2.60 ($P < 0.05$, corrected for multiple comparisons).

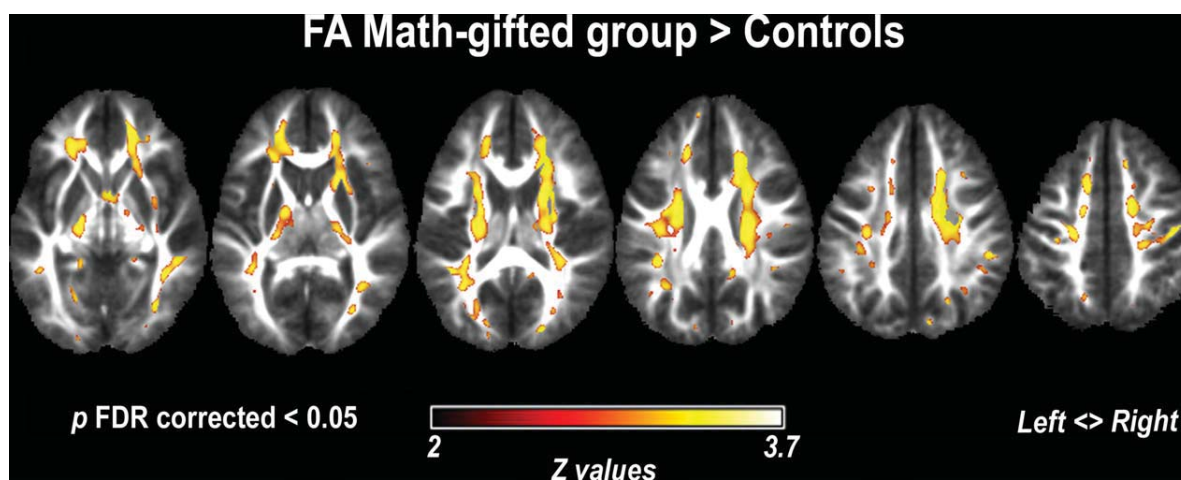


Figure 3.

Between-group contrast in voxel-wise analysis. The cluster shows significantly increased FA in the math-gifted group compared with the controls ($P < 0.05$ corrected for multiple comparisons), after adjustment for IQ. Significant clusters are

superimposed on the mean FA image in MNI space. The color bar shows the Z-score for this contrast. Increased FA was observed bilaterally in the prefrontal lobes, cortico-striatal tracts, and fronto-parietal fasciculus in math-gifted adolescents.

et al., 2003; Klingberg et al., 1997; Kroger et al., 2002; Newman et al., 2003; Prabhakaran et al., 1997; Smith and Jonides, 1999). Increased FA in the corpus callosum in atypical hemispheric dominance (bilateralism) and high IQ might enhance the capacity for information processing between hemispheres.

The greater abilities in visuospatial processing shown by math-gifted subjects might be related to increased FA in the forceps major and splenium, which connect both the right and the left parieto-occipital cortices [Fryer et al., 2008; Harris et al., 2000.; Just et al., 2001; Klingberg, 2006; Knauff et al., 2002; Owen et al., 1996; Todd and Marois, 2004; Van den Heuvel et al., 2003]. The development of inter-parietal white matter junction is also important for mathematical skills [Cantlon et al., 2011; Matejko et al., in press; Tsang et al., 2009]. Enhanced white matter organization in the frontal and parietal lobes might underlie high-level cognition with improved visuospatial working memory, mathematical, and executive capabilities.

The between-group differences observed in the FA of the corpus callosum could represent a facilitated communication between hemispheres and might lead to enhanced functional bilateralism [O'Boyle et al., 1991, 1995; Singh and O'Boyle, 2004]. The activation of both hemispheres, as observed in previous fMRI studies [Desco et al., 2011], and the interactions between them are essential for integration of information and complex logical reasoning [Dehaene et al., 1999]. Enhanced integration of information between hemispheres in children with high intellectual capabilities might be due to corpus callosum microstructure [Prescott et al., 2010].

Intrahemispheric White Matter Microstructure in Math-Giftedness

Math-gifted subjects showed increased FA bilaterally in tracts connecting the frontal lobes with the temporo-parietal cortices, after adjustment for the IQ effect. Data from previous functional neuroimaging studies [Christoff et al., 2001; Kroger et al., 2002; Newman et al., 2003; Prabhakaran et al., 1997] and DTI studies [Klingberg, 2006; Schmithorst et al., 2005] converge toward a bilateral fronto-parietal network as a neural substrate of enhanced information processing and intelligence [Jung and Haier, 2007]. Increased white matter organization in frontal lobe tracts supports enhanced high-level cognition functions, which contribute to improved cognitive performance in working memory, fluency, and executive functioning [Burzynska et al., 2011; Nagy et al., 2004]. The increased white matter organization of the frontal lobe in math-gifted adolescents could be one of the neurobiological traits underlying math giftedness.

The major tract that connects frontal lobes and temporo-parietal regions is the superior longitudinal fasciculus, which is crucial for integration of information within hemispheres. The math-gifted group showed higher white matter integrity in regions of the superior longitudinal fasciculus adjacent to the inferior parietal lobule. In our previous fMRI study with this study sample, we reported that major between-group differences appeared with more complex tasks, mainly in the frontal cortex and right inferior parietal lobule [Desco et al., 2011]. The inferior parietal lobule (BA40) has been associated with multimodal information processing, mental imagery [Wolbers et al.,

◆ White Matter Microstructure ◆

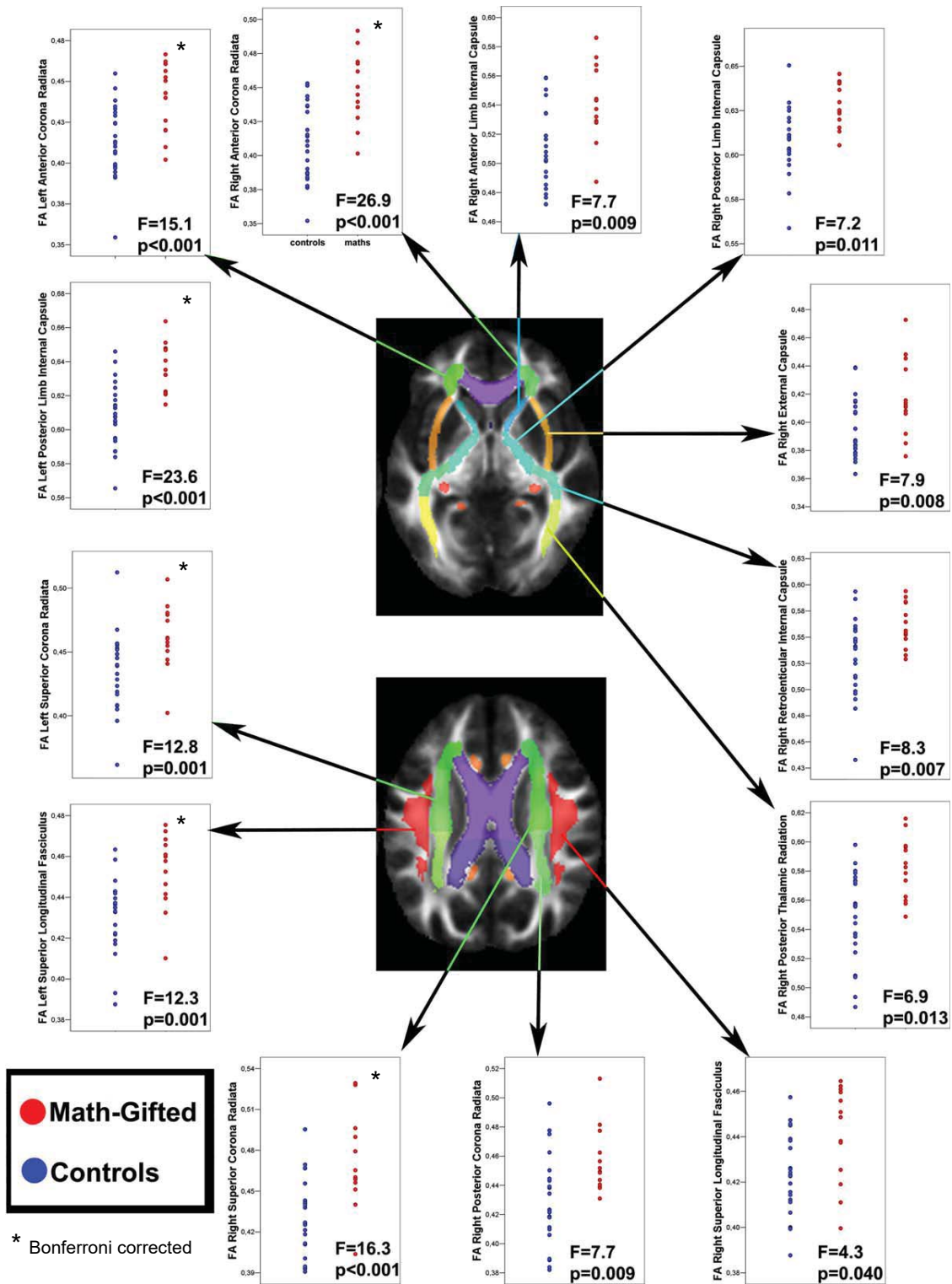


Figure 4.

Between-group differences in the atlas-based parcellation analysis in native space. The graphs represent anatomical regions in which the math-gifted group (in red) showed significantly more FA than controls (in blue), after adjustment for the potential effects of IQ.

2006], and creativity [Finke, 1996; Takeuchi et al., 2010]. Recent neuroimaging literature (using either fMRI or DTI) showed the crucial role that parietal lobules play in mathematical processing, such as arithmetical or calculation tasks [Cantlon et al., 2011; Dehaene et al., 2003; Hoppe et al., 2012; Matejko et al., in press; Tsang et al., 2009; van Eimeren et al., 2008, 2010].

Some studies of the neurobiological traits of math-giftedness show the anterior cingulate gyrus to be a key structure [O'Boyle, et al., 2005; Prescott et al., 2010]. Our results did not show a group effect in this region. Functional connectivity studies could reveal statistically correlated regions with few direct structural connections between them. Functional correlations can be mediated by indirect structural connections (i.e., via a third region). Therefore, the potential role played by the anterior cingulate gyrus as a hub in functional connectivity does not necessarily lead to increased FA.

Mathematical thinking requires contributions from both academic and creative capabilities, and gifted subjects showed neurobiological characteristics that encompassed these requirements. The greater activation of the frontoparietal network observed in our previous study [Desco et al., 2011] was consistently accompanied by increased white matter organization in anatomical connections between the frontal and the parietal lobes.

Math-Giftedness and IQ

Math-giftedness can be assumed to partially correlate with a high IQ, although it does not seem to be the same construct [Kalbfleisch, 2004]. Our results suggest that increased anatomical intrahemispheric connectivity in the fronto-parietal network may underlie math-giftedness, independently of IQ, which in turn seems more related to interhemispheric connectivity. These findings were replicated in the comparison of the math-gifted subjects with a subsample of nine high IQ-matched controls. Both the frontoparietal and frontostriatal white matter tracts are associated with "giftedness," and FA of the genu of the corpus callosum was moderately correlated with IQ in this subsample. This replication of the results, albeit with a lower number of cases, shows the robustness of the detected effects. The findings support the existence of a different substrate for "IQ" and "Giftedness."

A functional connectivity study using Structural Equation Modeling performed by Prescott et al. [2010] reported results that were consistent with ours: heightened intrahemispheric frontoparietal connectivity together with enhanced interhemispheric frontal connectivity. Furthermore, our results suggest the existence of neurobiological correlates underlying the enhanced connectivity in gifted subjects and segregate the effect of "IQ" and "Giftedness" per se.

Our findings support that "IQ" and "Giftedness" are different concepts. We suggest that gifted adolescents,

regardless of the advantages of their high IQ, have a different brain structure that is more associated with an innovative way of processing information during complex cognitive tasks or novel problem solving. Increased FA in frontoparietal and frontostriatal networks was not observed in controls with a similar IQ to that of the gifted group.

Math-gifted subjects were selected for the ESTALMAT program, which in comparison with SAT-Math emphasizes problem solving by creative thinking rather than using concepts and previous expertise and knowledge gained at school. Although the neural substrate that underlies the relationship between math-giftedness and creativity is still unclear, "creative thinking" is implicit in the concept of Giftedness. Indeed, the neurobiological and related cognitive characteristics of gifted people have been combined in a neuropsychological model of high creative intelligence [Geake and Dodson, 2005; Geake and Hansen, 2005]. This model of creative intelligence features fluid analogizing, analogies with several plausible but no necessary correct solutions [Hofstadter, 1995, 2001], as the vehicle by which dynamic information processing occurs in the brain. Creative thinking has also been related to enhanced interhemispheric and intrahemispheric white matter organization along the corpus callosum and fronto-parietal areas [Takeuchi et al., 2010]. Connections between the prefrontal lobes and basal ganglia are thought to enable key processes of creativity, such as problem solving [Kalbfleisch, 2004; Takeuchi et al., 2010]. Some authors reported a link between intelligence and creativity [Carroll, 1993; Jung et al., 2010; Sternberg, 2000, 2001]. Jung et al. observed a correlation between FSIQ and the composite creativity index in divergent thinking [Jung et al., 2010]. The enhanced white matter organization in fronto-parietal regions observed in the math-gifted group would facilitate processing of information that is crucial for higher intellectual capabilities and for creativity.

Our study has several limitations. With regard to cognitive characterization of the two groups, the selection of math-gifted subjects was based solely on their performance in the ESTALMAT admission tests, which examine additional cognitive abilities, especially creativity (see "Methods"). Consequently, the definition of math-giftedness used in this study is based on the criteria established by ESTALMAT. As is the case for the definition of IQ, our definition of "giftedness" in this work is purely operational. Both depend on the outcome of the (very different) tests used to assess them. Most of the studies cited in this article reported conclusions about math-gifted adolescents selected using other tests, such as SAT-Math, which assess pure mathematical skills.

Because the controls never took the ESTALMAT tests, we cannot rule out the possibility that some of them are math-gifted. However, we can realistically assume that

◆ White Matter Microstructure ◆

their proportion in our sample is negligible, given the low number of math-gifted subjects in the population.

In the statistical analyses, we acknowledge that linear covariance in the ANCOVA model may be subject to limitations, because the groups have different IQ ranges. Nevertheless, a verification run using IQ-matched subanalyses showed the same results.

A further limitation of the study is that the groups were not matched by gender. Developmental differences have been observed in the brains of boys and girls [Tang et al., 2010]. As an additional verification, we repeated the whole analysis for the male subsample only, and the results remained unchanged. In fact, after checking potential interactions such as “Group \times Gender” and “IQ \times Gender,” we did not observe any significant effect. We used an estimated IQ, which is only an approximation of the FSIQ. However, this estimated score has been validated for the normal population (see “Cognitive Assessment” in “Methods”). The relationship between math-giftedness and creativity warrants further assessment in neuroimaging studies.

CONCLUSIONS

Our results suggest that IQ and math-giftedness correlate differently with white matter microstructure. In the whole sample, IQ correlated with FA positively in a large part of the corpus callosum. Moreover, math-gifted subjects showed higher FA than controls (independently of IQ) in fronto-parietal and fronto-striatal association tracts, as well as in the forceps of the corpus callosum.

Our results support the hypothesis that white matter organization in math-gifted adolescents is different both in fronto-parietal tracts and in the corpus callosum. This finding could explain the functional bilateralism in fronto-parietal networks observed in math-gifted subjects in previous fMRI studies. Math-gifted subjects are qualitatively and quantitatively different, not only in terms of brain activation but also in terms of white matter organization in brain regions that underlie high-level cognitive processes and creativity.

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◆ White Matter Microstructure ◆

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Appendix Chapter 4

In this appendix, we intend to demonstrate that IQ scores have low effect on FA in our analysis. We present, firstly the voxel-wise analysis using a subsample of controls with high IQ (n=9) and the math-gifted subjects (n=13), secondly we assess the potential effect of ‘gender; and ;age; on the FA data.

Figure 4.A1. The main differences between groups survive subsampling based on the same gifted subjects vs. high IQ-matched controls; however the p-values are not corrected for multiple comparisons.

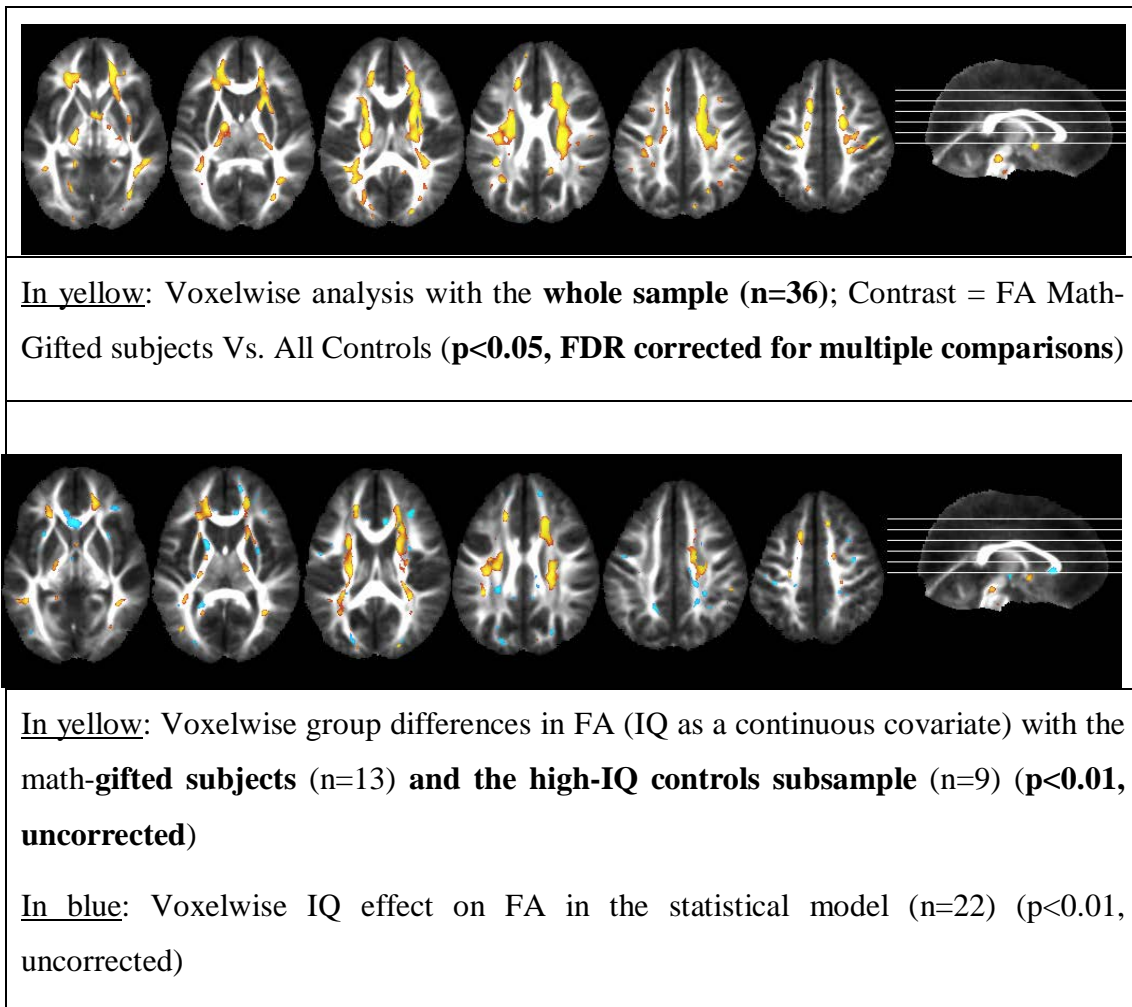


Table 3. A1. Analysis of Variance (univariate general linear model in SPSS v.13). Main effects of fixed factor = “Group” in the ROI analysis. First, the contrast Math-gifted (n=13) vs. Controls (n=23). On the right, the contrast Math-gifted group (n=13) vs. High-IQ Controls (n=9).

Dependent Variable	GROUP (n=13 vs. 23)		Math-Gifted (n=13) vs. Controls High IQ (n=9)	
	F	Sig.	F	Sig.
FA Whole Corpus callosum	7,60	0,0093	2,46	0,1320
FA Genu CC	5,90	0,0205	2,61	0,1220
FA Body CC	6,36	0,0165	1,62	0,2170
FA Splenium CC	6,22	0,0176	2,02	0,1710
FA Corticospinal R	1,80	0,189	0,04	0,837
FA Corticospinal L	9,31	0,0044	2,99	0,0990
FA Anterior Limb Internal Capsule R	12,21	0,0013	11,87	0,0030
FA Anterior Limb Internal Capsule L	5,53	0,0247	2,66	0,1190
FA Posterior Limb Internal Capsule R	12,35	0,0013	8,64	0,0080
FA Posterior Limb Internal Capsule L	21,59	0,0000	25,60	0,0000
FA Retrolenticular part Internal Capsule R	7,16	0,0114	12,87	0,0020
FA Retrolenticular part Internal Capsule L	5,15	0,0297	11,00	0,0030
FA Anterior Corona Radiata R	18,21	0,0001	20,11	0,0000
FA Anterior Corona Radiata L	11,62	0,0017	14,12	0,0010
FA Superior Corona Radiata R	15,01	0,0005	18,34	0,0000
FA Superior Corona Radiata L	6,84	0,0132	13,16	0,0020
FA Posterior Corona Radiata R	8,32	0,0068	20,13	0,0000
FA Posterior Corona Radiata L	3,92	0,056	9,29	0,006
FA Posterior Thalamic Radiation R	12,47	0,0012	16,32	0,0010
FA Posterior Thalamic Radiation L	6,10	0,0187	9,40	0,006
FA Sagital Striatum R (ILF, IFOF)	4,62	0,0388	9,58	0,006
FA Sagital Striatum L (ILF, IFOF)	0,61	0,442	2,07	0,165
FA External Capsule R	7,25	0,0109	12,43	0,0020
FA External Capsule L	0,61	0,442	3,50	0,076
FA Cingulum R	0,11	0,746	0,03	0,873
FA Cingulum L	2,12	0,155	2,22	0,151
FA Superior Longitudinal Fasciculus R	7,75	0,0087	6,41	0,0200
FA Superior Longitudinal Fasciculus L	11,21	0,0020	15,67	0,0010
FA Superior Fronto-occipital Fasciculus R	7,22	0,0111	3,50	0,0760
FA Superior Fronto-occipital Fasciculus L	1,08	0,307	1,69	0,208
FA Uncinate R	1,73	0,197	1,73	0,203
FA Uncinate L	4,00	0,054	7,25	0,014

R= Right Hemisphere; L= Left Hemisphere

In red: Significant p-values; Bold-faced: p-values bonferroni corrected (p=0.05/34=0.0015)

Table 3. A2 ANCOVA (univariate general linear model in SPSS v.13). Main effects of fixed factor = “Group”, and continuous covariate = “IQ”. In the N=22 (Math-gifted 13/Controls High IQ 9) analysis: No significant differences in IQ between groups were observed. No Group*IQ interaction was observed in any analysis (omitted in these models).

Dependent Variable	Whole Sample (n=13+23)				Math-Gifted (n=13) vs. Controls High IQ (n=9)			
	GROUP		IQ		GROUP		IQ	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
FA Whole Corpus callosum	0,94	0,339	3,04	0,090	1,00	0,330	1,33	0,263
FA Genu CC	1,23	0,276	1,17	0,287	1,31	0,266	0,70	0,414
FA Body CC	0,52	0,478	3,51	0,070	0,54	0,470	1,26	0,276
FA Splenium CC	0,60	0,444	3,01	0,092	0,73	0,405	1,40	0,251
FA Corticospinal R	0,00	0,948	2,08	0,159	0,05	0,823	0,01	0,920
FA Corticospinal L	1,74	0,196	2,33	0,136	2,23	0,152	0,02	0,890
FA Anterior Limb Internal Capsule R	7,66	0,009	0,08	0,782	7,83	0,011	0,80	0,382
FA Anterior Limb Internal Capsule L	1,06	0,310	1,23	0,275	0,83	0,374	2,73	0,115
FA Posterior Limb Internal Capsule R	7,28	0,011	0,02	0,877	6,55	0,019	0,04	0,845
FA Posterior Limb Internal Capsule L	23,57	0,0000	3,54	0,069	23,00	0,0001	0,32	0,576
FA Retrolenticular part Internal Capsule R	8,29	0,007	1,67	0,205	9,86	0,005	0,04	0,844
FA Retrolenticular part Internal Capsule L	4,66	0,038	0,50	0,482	7,71	0,012	0,31	0,583
FA Anterior Corona Radiata R	26,91	0,0000	6,81	0,014	23,57	0,0001	2,32	0,144
FA Anterior Corona Radiata L	15,08	0,0005	3,49	0,071	14,76	0,0011	0,98	0,335
FA Superior Corona Radiata R	16,27	0,0003	2,58	0,117	14,91	0,0011	0,00	0,951
FA Superior Corona Radiata L	12,77	0,0011	5,12	0,030	13,55	0,0016	0,84	0,372
FA Posterior Corona Radiata R	7,74	0,009	0,89	0,352	13,41	0,0017	2,21	0,154
FA Posterior Corona Radiata L	2,90	0,098	0,13	0,720	5,78	0,027	1,03	0,322
FA Posterior Thalamic Radiation R	15,54	0,0004	3,32	0,077	18,15	0,0004	1,58	0,224
FA Posterior Thalamic Radiation L	6,90	0,013	1,35	0,254	7,61	0,013	0,00	0,978
FA Sagital Striatum R (ILF, IFOF)	4,17	0,049	0,45	0,507	8,29	0,010	0,07	0,801
FA Sagital Striatum L (ILF, IFOF)	2,04	0,163	1,60	0,214	1,78	0,198	0,01	0,913
FA External Capsule R	7,95	0,008	1,42	0,242	8,61	0,009	0,44	0,516
FA External Capsule L	1,09	0,304	0,50	0,486	2,24	0,151	0,23	0,637
FA Cingulum R	0,28	0,599	1,38	0,249	0,13	0,720	0,31	0,587
FA Cingulum L	1,20	0,282	0,00	0,978	1,44	0,244	0,12	0,728
FA Superior Longitudinal Fasciculus R	4,31	0,046	0,00	0,973	4,65	0,044	0,09	0,770
FA Superior Longitudinal Fasciculus L	12,28	0,0013	2,08	0,158	13,60	0,0016	0,11	0,743
FA Superior Fronto-occipital Fasciculus R	2,60	0,117	0,33	0,567	3,06	0,096	0,03	0,856
FA Superior Fronto-occipital Fasciculus L	2,15	0,152	1,08	0,307	2,07	0,167	0,43	0,518
FA Uncinate R	0,78	0,382	0,02	0,898	0,76	0,394	0,70	0,413
FA Uncinate L	3,22	0,082	0,22	0,639	6,11	0,023	0,02	0,882

R= Right Hemisphere; L= Left Hemisphere

In red: Significant p-values;

Bold-faced: p-values Bonferroni corrected (p=0.05/34=0.0015)

Figure 4.A2. Gender Effects on FA data: Females did not increase noise or confound the “group” and “IQ” effects in these analyses. The map obtained with males only and the map obtained with the whole sample are basically the same.

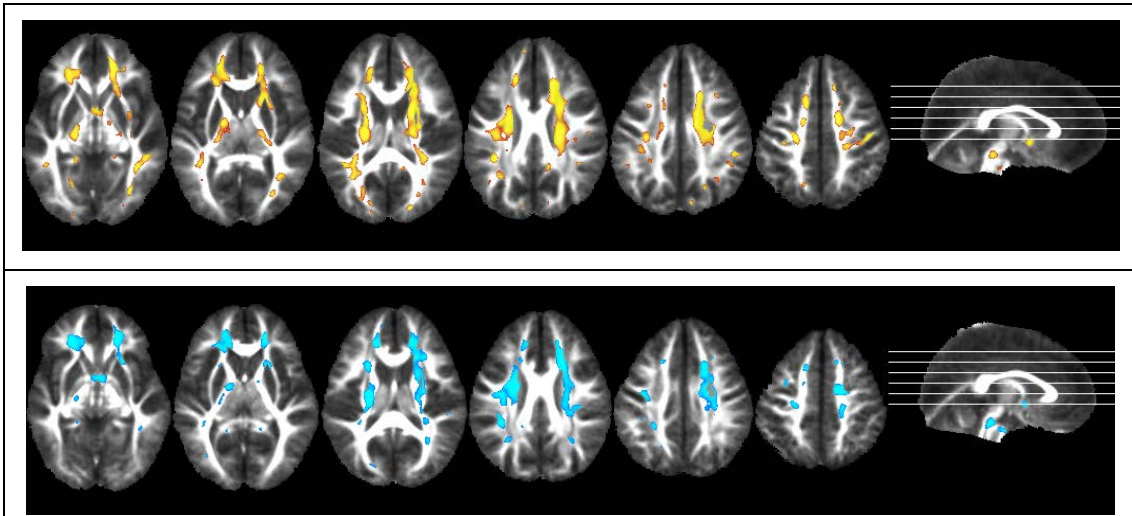


Fig. In yellow: Voxelwise analysis with the **whole sample (n=36)**; contrast = FA Math > Controls ($p < 0.05$, FDR). In blue: Voxelwise analysis with **Males (n=27)**; contrast = FA Males Math > Male controls ($p < 0.05$, uncorrected)

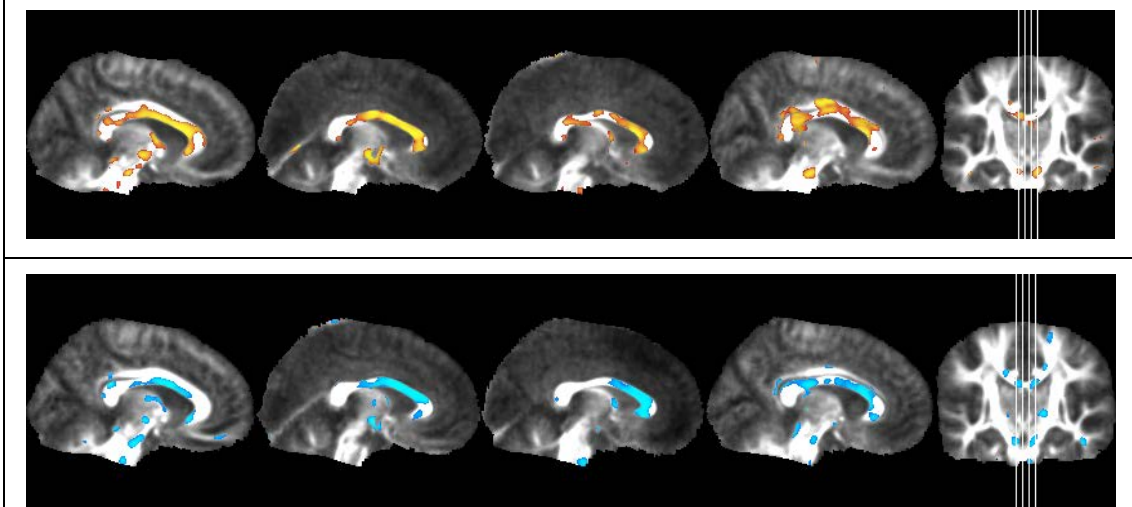


Fig. In yellow: Voxelwise Correlation FA and IQ with the whole sample (n=36) ($p < 0.05$, uncorrected). In blue: Voxelwise Correlation FA and IQ with males (n=27) ($p < 0.05$, uncorrected)

Table 4.A3. ANCOVAs with 2 factors ('gender' and 'group') and one covariate (IQ). There is no significant main effect of "Gender" on the white matter tracts. We omitted the Gender factor from the final model presented in the article.

Whole Sample (n=36)	ANCOVA 2 FACTORS: Group & Gender; COVARIABLE: IQ						ANCOVA 1 FACTOR: Group; COVARIABLE: IQ			
	GROUP		IQ		GENDER		GROUP		IQ	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.
FA Whole Corpus callosum	0,358	0,554	3,599	0,067	3,345	0,077	0,943	0,339	3,042	0,090
FA Genu CC	0,664	0,421	1,354	0,253	1,803	0,189	1,227	0,276	1,172	0,287
FA Body CC	0,117	0,734	4,125	0,051	3,351	0,076	0,515	0,478	3,510	0,070
FA Splenium CC	0,179	0,675	3,491	0,071	2,862	0,100	0,599	0,444	3,011	0,092
FA Corticospinal R	0,020	0,887	2,221	0,146	0,973	0,331	0,004	0,948	2,079	0,159
FA Corticospinal L	1,068	0,309	2,577	0,118	1,633	0,211	1,739	0,196	2,331	0,136
FA Anterior Limb Internal Capsule R	5,789	0,022	0,035	0,853	4,012	0,054	7,657	0,009	0,078	0,782
FA Anterior Limb Internal Capsule L	0,494	0,487	1,474	0,234	2,446	0,128	1,065	0,310	1,234	0,275
FA Posterior Limb Internal Capsule R	5,652	0,024	0,007	0,934	2,107	0,156	7,280	0,011	0,024	0,877
FA Posterior Limb Internal Capsule L	20,778	0,000	3,341	0,077	0,561	0,459	23,573	0,000	3,541	0,069
FA Retrolenticular part Internal Capsule R	7,273	0,011	1,570	0,219	0,153	0,698	8,291	0,007	1,668	0,205
FA Retrolenticular part Internal Capsule L	4,992	0,033	0,545	0,466	0,455	0,505	4,658	0,038	0,505	0,482
FA Anterior Corona Radiata R	24,171	0,000	6,507	0,016	0,199	0,658	26,910	0,000	6,808	0,014
FA Anterior Corona Radiata L	15,397	0,000	3,575	0,068	0,537	0,469	15,079	0,000	3,492	0,071
FA Superior Corona Radiata R	14,531	0,001	2,448	0,128	0,148	0,703	16,271	0,000	2,584	0,117
FA Superior Corona Radiata L	11,216	0,002	4,875	0,035	0,255	0,617	12,775	0,001	5,120	0,030
FA Posterior Corona Radiata R	6,582	0,015	0,812	0,374	0,382	0,541	7,744	0,009	0,890	0,352
FA Posterior Corona Radiata L	2,511	0,123	0,117	0,735	0,074	0,787	2,901	0,098	0,131	0,720
FA Posterior Thalamic Radiation R	14,094	0,001	3,178	0,084	0,043	0,837	15,538	0,000	3,322	0,077
FA Posterior Thalamic Radiation L	6,114	0,019	1,271	0,268	0,083	0,775	6,904	0,013	1,346	0,254
FA Sagittal Striatum R (ILF, IFOF)	4,559	0,041	0,494	0,487	0,532	0,471	4,168	0,049	0,450	0,507
FA Sagittal Striatum L (ILF, IFOF)	1,851	0,183	1,543	0,223	0,004	0,951	2,035	0,163	1,603	0,214
FA External Capsule R	6,921	0,013	1,330	0,257	0,197	0,661	7,954	0,008	1,422	0,242
FA External Capsule L	1,010	0,322	0,479	0,494	0,000	0,997	1,092	0,304	0,496	0,486
FA Cingulum R	0,272	0,605	1,339	0,256	0,002	0,962	0,282	0,599	1,378	0,249
FA Cingulum L	1,033	0,317	0,000	0,985	0,032	0,860	1,196	0,282	0,001	0,978
FA Superior Longitudinal Fasciculus R	4,416	0,044	0,003	0,955	0,205	0,654	4,315	0,046	0,001	0,973
FA Superior Longitudinal Fasciculus L	11,732	0,002	2,052	0,162	0,053	0,819	12,281	0,001	2,084	0,158
FA Superior Fronto-occipital Fasciculus R	2,398	0,131	0,324	0,573	0,000	0,991	2,595	0,117	0,334	0,567
FA Superior Fronto-occipital Fasciculus L	2,048	0,162	1,051	0,313	0,009	0,926	2,148	0,152	1,076	0,307
FA Uncinate R	1,576	0,218	0,002	0,966	3,000	0,093	0,784	0,382	0,017	0,898
FA Uncinate L	3,672	0,064	0,262	0,612	0,663	0,422	3,220	0,082	0,224	0,639

R= Right Hemisphere; L= Left Hemisphere

Table 4.A4. ANCOVAs with 2 factors ('gender' and 'group'); including the interaction between factors, and one covariate (IQ). There is no main effect of gender and there is no significant interaction Group*Gender. We omitted Gender and the interaction Group*Gender from the final model.

Whole Sample (n=36)	ANCOVA 2 FACTORS: Group & Gender; COVARIABLE: IQ						INTERACTIONS INCLUDED	
	GROUP		IQ		GENDER		GROUP*GENDER	
	F	Sig.	F	Sig.	F	Sig.	F	Sig.
FA Whole Corpus callosum	0,545	0,466	3,344	0,077	3,321	0,078	0,250	0,620
FA Genu CC	0,959	0,335	1,209	0,280	1,817	0,187	0,373	0,546
FA Body CC	0,493	0,488	3,780	0,061	3,465	0,072	1,005	0,324
FA Splenium CC	0,033	0,856	3,548	0,069	2,739	0,108	0,279	0,601
FA Corticospinal R	0,002	0,967	2,088	0,159	0,958	0,335	0,053	0,820
FA Corticospinal L	0,497	0,486	2,672	0,112	1,550	0,222	0,388	0,538
FA Anterior Limb Internal Capsule R	5,602	0,024	0,049	0,827	3,965	0,055	0,204	0,654
FA Anterior Limb Internal Capsule L	0,918	0,345	1,296	0,264	2,498	0,124	0,662	0,422
FA Posterior Limb Internal Capsule R	5,564	0,025	0,015	0,904	2,101	0,157	0,245	0,624
FA Posterior Limb Internal Capsule L	14,985	0,001	3,052	0,091	0,517	0,478	0,666	0,421
FA Retrolenticular part Internal Capsule R	8,608	0,006	1,809	0,188	0,184	0,671	1,273	0,268
FA Retrolenticular part Internal Capsule L	6,006	0,020	0,668	0,420	0,413	0,525	1,017	0,321
FA Anterior Corona Radiata R	20,261	0,000	6,300	0,018	0,195	0,662	0,008	0,929
FA Anterior Corona Radiata L	15,923	0,000	3,844	0,059	0,492	0,488	0,936	0,341
FA Superior Corona Radiata R	9,646	0,004	2,179	0,150	0,124	0,728	1,215	0,279
FA Superior Corona Radiata L	8,129	0,008	4,551	0,041	0,233	0,633	0,284	0,598
FA Posterior Corona Radiata R	8,479	0,007	1,034	0,317	0,445	0,510	1,790	0,191
FA Posterior Corona Radiata L	2,219	0,146	0,120	0,732	0,074	0,787	0,017	0,898
FA Posterior Thalamic Radiation R	18,958	0,000	4,027	0,054	0,077	0,783	3,736	0,062
FA Posterior Thalamic Radiation L	9,379	0,005	1,714	0,200	0,127	0,724	3,305	0,079
FA Sagittal Striatum R (ILF, IFOF)	5,893	0,021	0,636	0,431	0,485	0,491	1,345	0,255
FA Sagittal Striatum L (ILF, IFOF)	2,922	0,097	1,790	0,191	0,010	0,922	1,347	0,255
FA External Capsule R	7,983	0,008	1,521	0,227	0,226	0,638	1,055	0,312
FA External Capsule L	1,436	0,240	0,551	0,463	0,001	0,979	0,520	0,476
FA Cingulum R	0,002	0,968	1,121	0,298	0,009	0,927	1,889	0,179
FA Cingulum L	1,466	0,235	0,006	0,939	0,040	0,843	0,529	0,472
FA Superior Longitudinal Fasciculus R	5,149	0,030	0,016	0,900	0,179	0,675	0,765	0,388
FA Superior Longitudinal Fasciculus L	12,212	0,001	2,235	0,145	0,041	0,842	0,796	0,379
FA Superior Fronto-occipital Fasciculus R	2,129	0,155	0,300	0,588	0,000	0,988	0,018	0,894
FA Superior Fronto-occipital Fasciculus L	2,494	0,124	1,145	0,293	0,005	0,944	0,489	0,490
FA Uncinate R	3,339	0,077	0,008	0,930	2,977	0,094	2,743	0,108
FA Uncinate L	4,616	0,040	0,347	0,560	0,612	0,440	0,977	0,331

R= Right Hemisphere; L= Left Hemisphere

Figure 4.A3. Age Effects on FA data. In the voxelwise analysis, there were no age-related effects (p-value uncorrected) on FA that modified the group differences analysis (p-value corrected for multiple comparisons).

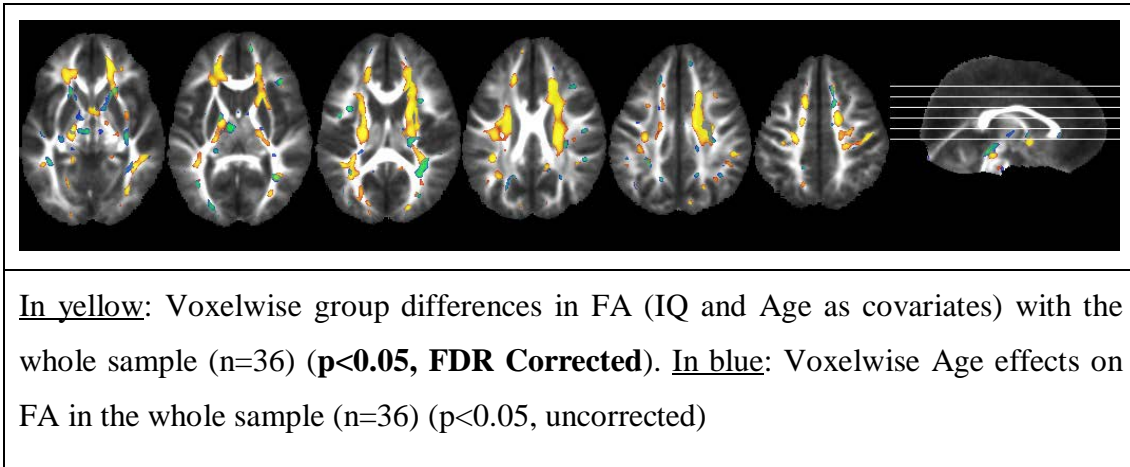


Table 4.A5. There was a significant effect of Age on the left corticospinal tract, right posterior thalamic radiation, and right sagittal striatum. Only the effect on the sagittal striatum modified the main effect of “Group”.

Whole Sample (n=36)	ANCOVA 1 FACTOR: Group; COVARIABLES: IQ & AGE						ANCOVA 1 FACTOR: Group; COVARIABLE: IQ			
	GROUP		IQ		AGE (months)		GROUP		IQ	
Dependent Variable	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.
FA Whole Corpus callosum	0,909	0,347	2,953	0,095	0,003	0,960	0,943	0,339	3,042	0,090
FA Genu CC	1,215	0,279	1,147	0,292	0,024	0,878	1,227	0,276	1,172	0,287
FA Body CC	0,532	0,471	3,428	0,073	0,043	0,837	0,515	0,478	3,510	0,070
FA Splenium CC	0,504	0,483	2,893	0,099	0,103	0,750	0,599	0,444	3,011	0,092
FA Corticospinal R	0,038	0,846	2,067	0,160	3,412	0,074	0,004	0,948	2,079	0,159
FA Corticospinal L	1,121	0,298	2,418	0,130	5,411	0,027	1,739	0,196	2,331	0,136
FA Anterior Limb Internal Capsule R	6,692	0,014	0,100	0,754	1,421	0,242	7,657	0,009	0,078	0,782
FA Anterior Limb Internal Capsule L	0,800	0,378	1,166	0,288	0,746	0,394	1,065	0,310	1,234	0,275
FA Posterior Limb Internal Capsule R	6,401	0,017	0,034	0,854	0,952	0,337	7,280	0,011	0,024	0,877
FA Posterior Limb Internal Capsule L	21,770	0,000	3,706	0,063	1,340	0,256	23,573	0,000	3,541	0,069
FA Retrolenticular part Internal Capsule R	7,234	0,011	1,939	0,173	3,394	0,075	8,291	0,007	1,668	0,205
FA Retrolenticular part Internal Capsule L	4,387	0,044	0,492	0,488	0,004	0,948	4,658	0,038	0,505	0,482
FA Anterior Corona Radiata R	25,236	0,000	6,653	0,015	0,073	0,788	26,910	0,000	6,808	0,014
FA Anterior Corona Radiata L	15,519	0,000	3,363	0,076	0,660	0,422	15,079	0,000	3,492	0,071
FA Superior Corona Radiata R	15,286	0,000	2,521	0,122	0,028	0,868	16,271	0,000	2,584	0,117
FA Superior Corona Radiata L	11,770	0,002	5,053	0,032	0,204	0,655	12,775	0,001	5,120	0,030
FA Posterior Corona Radiata R	6,800	0,014	0,956	0,335	1,173	0,287	7,744	0,009	0,890	0,352
FA Posterior Corona Radiata L	2,735	0,108	0,128	0,723	0,002	0,963	2,901	0,098	0,131	0,720
FA Posterior Thalamic Radiation R	14,486	0,001	3,944	0,056	4,688	0,038	15,538	0,000	3,322	0,077
FA Posterior Thalamic Radiation L	6,184	0,018	1,365	0,251	0,406	0,529	6,904	0,013	1,346	0,254
FA Sagittal Striatum R (ILF, IFOF)	3,327	0,077	0,689	0,413	8,466	0,007	4,168	0,049	0,450	0,507
FA Sagittal Striatum L (ILF, IFOF)	1,913	0,176	1,557	0,221	0,003	0,958	2,035	0,163	1,603	0,214
FA External Capsule R	6,965	0,013	1,529	0,225	1,457	0,236	7,954	0,008	1,422	0,242
FA External Capsule L	0,943	0,339	0,497	0,486	0,120	0,731	1,092	0,304	0,496	0,486
FA Cingulum R	0,188	0,667	1,394	0,246	0,374	0,545	0,282	0,599	1,378	0,249
FA Cingulum L	1,074	0,308	0,001	0,973	0,046	0,832	1,196	0,282	0,001	0,978
FA Superior Longitudinal Fasciculus R	3,545	0,069	0,006	0,938	2,172	0,150	4,315	0,046	0,001	0,973
FA Superior Longitudinal Fasciculus L	11,756	0,002	2,012	0,166	0,008	0,930	12,281	0,001	2,084	0,158
FA Superior Fronto-occipital Fasciculus R	2,262	0,142	0,309	0,582	0,260	0,614	2,595	0,117	0,334	0,567
FA Superior Fronto-occipital Fasciculus L	2,100	0,157	1,035	0,317	0,020	0,888	2,148	0,152	1,076	0,307
FA Uncinate R	0,913	0,346	0,021	0,885	0,378	0,543	0,784	0,382	0,017	0,898
FA Uncinate L	4,147	0,050	0,190	0,666	2,435	0,129	3,220	0,082	0,224	0,639

R= Right Hemisphere; L= Left Hemisphere

Chapter 5. Cortical Morphometry in Fronto-Parietal and Default Mode Networks in Math-Gifted Adolescents

This chapter has been submitted as original article:

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Abstract

Math-gifted subjects are characterized by above-age performance in intelligence tests, exceptional creativity, and high task commitment. Neuroimaging studies reveal enhanced functional brain organization and white matter microstructure in the fronto-parietal executive network of math-gifted individuals. However, the cortical morphometry of these subjects remains largely unknown. The main goal of this study was to compare the cortical morphometry of math-gifted adolescents with that of an age- and IQ-matched control group. We used surface-based methods to perform a vertex-wise analysis of cortical thickness and surface area. Our results show that math-gifted adolescents present a thinner cortex and a larger surface area in key regions of the fronto-parietal and default mode networks, which are involved in executive processing and creative thinking, respectively (all p-values < 0.05, cluster-wise probability corrected). The combination of reduced cortical thickness and larger surface area suggests above-age neural maturation of these networks in math-gifted individuals.

Keywords: Area, Cortex, Default mode, Fronto-parietal, Math-Giftedness, Thickness

5.1 Introduction

The bases of intelligence have been investigated for many years. In the last decade, new insights from brain imaging techniques have revealed a potential association between individual differences in intelligence (e.g. IQ, g-factor) and brain functioning and cortical morphometry (Jung and Haier 2007). In parallel, neuroimaging researchers have been trying to identify the neural bases that underlie giftedness. In broad terms, giftedness is a special form of intelligence that takes the form not only of higher IQ and enhanced executive functioning, but also of exceptional creativity (such as the production of novel and useful ideas) and higher motivation in specific traits (Renzulli 1978; Kießwetter 1985; Renzulli 1998; Kalbfleisch 2004; Sternberg and Davidson 2005; Sternberg 2010). When these abilities are applied to mathematical thinking, subjects are referred to as “math-gifted”.

Task-based functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) data support the existence of special characteristics of the fronto-parietal executive network (FPN) in math-gifted individuals. (O'Boyle M. W. et al. 2005; Lee et al. 2006; O'Boyle Michael W. 2008; Prescott et al. 2010; Desco et al. 2011; Hoppe et al. 2012; Navas-Sanchez et al. 2014). For instance, task-based fMRI studies on executive functioning and fluid reasoning detected enhanced functional bilateralism in math-gifted adolescents in the dorsolateral prefrontal cortex, parietal cortex (including the superior and inferior parietal regions), and anterior cingulate cortex (O'Boyle M. W. et al. 2005; Prescott et al. 2010; Desco et al. 2011). Likewise, a recent DTI study in math-gifted subjects (Navas-Sanchez et al. 2014) reported heightened connectivity between the left and right hemispheres, as well as enhanced intra-hemispheric white matter connectivity between the frontal and parietal cortices.

Several reports indicate that gifted individuals perform above their age in cognitive tests, thus suggesting a higher level of cognitive maturation than their same-age peers (O'Boyle M. W. and Benbow 1990; Alexander et al. 1996; Gross 2004; Geake 2008). This cognitive precocity, especially in terms of IQ and working memory, has been associated with particular neural features that are compatible with a higher level of maturation in the fronto-parietal executive network (Alexander et al. 1996; Geake 2008). Importantly, cortical morphometry has proven to be a good correlate of cognitive abilities, as well as a good indicator of neural maturity. On the one hand, studies in non-gifted subjects have reported the existence of relationships between measurements of cortical

thickness and surface area and high-level neuro-cognitive abilities such as IQ, g-factor, executive functioning, fluid reasoning or creativity (Fjell et al. 2006; Shaw et al. 2006; Narr et al. 2007; Luders et al. 2009; Jung et al. 2010; Tamnes et al. 2010b; Karama et al. 2011; Burzynska et al. 2012; Colom et al. 2013; Skranes et al. 2013; Schnack et al. 2014; Fjell et al. 2015). Broadly speaking, these associations indicate that higher cognitive ability corresponds with lower cortical thickness and higher surface area. On the other hand, developmental studies suggested that during adolescence, cortical thickness decreases and surface area increases (Aleman-Gomez et al. 2013). Furthermore, cross-sectional and longitudinal studies report different patterns of cortical maturation as a function of subject IQ (Shaw et al. 2006; Schnack et al. 2014). However, to our knowledge, the possible existence of cortical features that are specific to math-gifted individuals has not been explored.

In this study, we aim to describe the morphometric characteristics of the cortex of mathematically gifted adolescents. In order to ensure that IQ effects are not confounded with those of the construct of ‘giftedness’, the control subjects included in the study were group-matched for IQ level with the math-gifted subjects.

Based on prior studies of math-giftedness and previous data from normal subjects, we hypothesized that the cognitive precocity of giftedness would entail cortical features that are compatible with above-age brain maturation. More specifically, we predict that these differences would affect regions of the fronto-parietal executive network. In addition, since creativity skills are considered a central characteristic of giftedness (Renzulli 1978;1998; Sternberg and Davidson 2005; Geake 2008; Navas-Sanchez et al. 2014) and recent literature suggests that individual differences in creativity are associated with key nodes of the default mode network (DMN) (Takeuchi et al. 2011a; Jung et al. 2013), we also expect above-age morphometric characteristics in the DMN of math-gifted individuals.

5.2 Methods

5.2.1 Sample Description

The sample recruited for the study included 62 right-handed adolescents (aged between 11 and 15 years), of whom 13 were math-gifted subjects (5 females) and 49 were controls (22 females). From the 49 controls we selected a subsample of 21 subjects (6 females) who were group-matched in age and IQ with the math-gifted sample. In addition, 4 controls were excluded owing to movement during image acquisition; therefore, the final sample included 17 control subjects (6 females). All subjects had between 5-9 years of schooling in the Spanish education system. Subjects meeting the criteria for neurological disease, psychiatric disease, presence of MRI-incompatible bioimplants, or medical conditions were not included in the study. **Table 5. 1.** shows the demographic characteristics of the sample.

The math-gifted adolescents were recruited from the Stimulus of Mathematical Talent Program (ESTALMAT; <http://www.uam.es/proyectosinv/estalmat/>) of the Spanish Royal Academy of Mathematical, Physical, and Natural Sciences in Madrid. Candidates for the ESTALMAT program are children who are particularly good at mathematics and willing to participate in the program and are proposed by teachers and parents. The subjects underwent a screening process consisting of a personal interview and math-related tests.

Those who passed this preliminary assessment, underwent a second examination based on a variety of specific tests proposed by K. Kiesswetter (Kießwetter 1985). The objective of these tests is to detect complex mathematical abilities that could be categorized as cognitive, motivational, and creative. Specifically, the tests assess visuospatial thinking, intuition, creativity, abstraction, manipulation, and ability to manage thoughts as follows: (1) organizing materials; (2) recognizing patterns or rules; (3) changing the representation of the problem and recognizing patterns and rules in a new area; (4) comprehending and working with highly complex structures; (5) reversing and inverting processes; and (6) finding related problems (Heller et al. 2000). Test answers were examined by mathematicians who considered not only the correctness of the answers, but also the argumentation followed to achieve the solution. The tests chosen were as original as possible, in such a way that previous training would not imply a clear advantage. In contrast with other standardized measures such as SAT-Math (Scholastic Assessment Test, Mathematics Section), ESTALMAT emphasizes problem solving by creative

thinking, rather than using concepts and previous expertise gained at school (Navas-Sanchez et al. 2014).

The control group was selected based on their age and IQ and academic levels. IQ was estimated using the Vocabulary, Information, and Block Design subtests from the Spanish version of the Wechsler Intelligence Scale for Children—Revised. These tests show good correspondence with full-scale IQ (Silverstein 1985; Ringe et al. 2002) and are commonly used in the literature. The cognitive assessment was performed by a child neuropsychologist and a child psychiatrist, who also analyzed the subjects' school records.

The study was approved by the Hospital Ethics and Clinical Research Boards. Written informed consent was obtained from both subjects and their parents before the study was performed.

5.2.2 Magnetic Resonance Imaging Acquisition

Data were acquired with a Philips Intera 1.5 T MRI scanner (*Philips Medical Systems, Best, The Netherlands*). The details of the protocol were as follows: high-resolution structural image T1-weighted gradient-echo; repetition time [TR] = 25 ms; echo time [TE] = 9.2 ms; field of view [FOV] = 256 x 256 x 175; flip angle = 30°; voxel size = 1 x 1 x 1 mm³.

5.2.3 MRI Data Preprocessing

First, MRI scans were skull-stripped and tissue-segmented with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; available at: <http://www.fil.ion.ucl.ac.uk/spm>) using the VBM8 toolbox (available at: <http://dbm.neuro.uni-jena.de/vbm>). All the images were visually inspected and the skull was manually removed if necessary.

Second, we performed a vertex-wise analysis using surface-based methods to account for group differences in whole-brain cortical thickness and surface area. Briefly, we processed the structural images with the standard FreeSurfer pipeline (available at: <http://www.surfer.nmr.mgh.harvard.edu>, version 5.3), which constructs models of the cortical interfaces (white-grey matter and CSF-grey matter) for all the subjects in the native anatomical space (Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000).

Before the statistical analyses, cortical thickness and surface area maps were normalized to a standard space (MNI space) and smoothed using a Gaussian filter with a full-width at half maximum of 15 mm.

5.2.4 Statistical Analysis

Group differences in whole-brain measurements (grey matter volume, intracranial volume, white matter volume, mean thickness, surface area, and cortex volume) was based on non-parametric statistical methods, namely *Mann-Whitney U test*. Standardized effect sizes and confidence intervals of the differences (95% CI) were also reported. Gender differences were compared using Pearson's chi-square test. The results of the whole-brain measurements were controlled by the False Discovery Rate, FDR ($q < 0.05$) (Benjamini and Hochberg, 1995). The statistical significance in vertex-wise data (cortical thickness and surface area) was assessed using a 2-tailed 2-sample *t* test. Standardized effect sizes (Cohen's *d*) were also calculated in the vertex-wise maps.

A vertex-wise statistical analysis was carried out separately for both the left and right hemispheres. Correction for multiple comparisons used the cluster-wise probability method (CWP) (Hagler et al. 2006). A total of 10,000 Monte-Carlo random permutations were used to obtain a CWP value lower than 0.05.

Additionally, to ensure that group differences in gender and IQ were not confounders, we repeated group comparisons including gender and IQ as covariates. Furthermore, to exclude the potential effect of cortical volume, we also performed another ANCOVA with cortex volume (which is the product of thickness and area) as a covariate. The output of these models is reported in the Supplementary Material.

5.3 Results

5.3.1 Global Measurements

Compared with controls, math-gifted subjects presented larger intracranial volume ($d=0.83$), lower whole-brain mean cortical thickness ($d=0.91$), larger white matter volumes ($d=1.22$), and larger whole-brain surface area ($d=0.84$). There were no significant differences between math-gifted subjects and controls in total cortical volume (**Table 5. 1**).

5.3.2 Vertex-wise Analysis: Group Differences in Cortical Thickness

Vertex-wise cortical thickness analysis revealed thinning in the bilateral superior frontal gyrus, left medial prefrontal cortex, anterior cingulate cortex, left precuneus, left medial prefrontal cortex (mPFC), left orbitofrontal cortex, and right superior parietal cortex (**Table 5. 2**; **Figure 5. 1**) in math-gifted individuals. In addition, the Cohen's d maps (**Figure 5. 1**) of group differences revealed a large effect size for the right medial prefrontal cortex, the lateral orbitofrontal cortex, and the supramarginal gyrus ($d>0.8$). Compared with math-gifted subjects, the controls did not show a significant reduction in cortical thickness.

Measurement	Anatomical Region	Side	Cluster Size (mm²)	X	Y	Z	CWP
Cortical thickness							
	Superior parietal	RH	1339.62	17.6	-68.8	45.2	0.0315
	Superior frontal	RH	3901.20	7.5	6.6	65.6	0.0001
	Pars orbitalis	LH	2994.61	-44.1	41.3	-11.4	0.0001
	Superior frontal	LH	4543.72	-5.9	-2.7	59.8	0.0001
	Precuneus	LH	2266.05	-11.6	-62.6	21.8	0.0007
Surface area							
	Superior frontal	RH	3955.97	21.7	28	36.3	0.0001
	Lingual	RH	4188.24	6.6	-79.6	-4	0.0001
	Superior frontal	LH	3984.19	-21.9	9.9	48.7	0.0001
	Inferior parietal	LH	2833.52	-43.6	-75.8	14.5	0.0022

Table 5. 1. Vertex-wise analysis of cortical thickness and surface area. The anatomical coordinates indicate the location where math-gifted subjects showed significantly thinner cortex or significantly larger surface area in the corrected clusters (LH, left hemisphere; RH, right hemisphere). CWP: cluster-wise probability.

	Math-Gifted (n=13; 5 females)			High-IQ Controls (n=17; 6 females)			p-value	Cohen's d
	Median	Mean	SD	Median	Mean	SD		
Age (years)	14	13.23	0.7	13	13.15	1.2	0.885	0.08
Sex (females)		38%			35%		0.858	
Age range (years) [min-max]		[12-14]			[11-15]			
Estimated full-scale IQ	129	130	10.7	125	123	8.4	0.086	0.68
IQ range [min-max]		[112-149]			[112-137]			
Verbal IQ	120	125.08	12.1	114	120.35	17.5	0.413	0.31
Performance IQ	131	128.85	12.1	123	121.18	14.1	0.129	0.58
Intracranial volume (cm ³)		1485.12	98.32		1392.29	115.76	0.028	0.83
Total grey matter volume (cm ³)		592.17	42.42		570.58	45.41	0.195	0.49
LH grey matter volume (cm ³)		297.44	20.65		286.70	23.53	0.202	0.48
RH grey matter volume (cm ³)		294.73	22.03		283.88	22.15	0.193	0.49
Total white matter volume (cm ³)		456.89	34.56		424.37	39.03	0.025	0.87
LH white matter volume (cm ³)		225.30	17.32		210.62	19.89	0.043	0.78
RH white matter volume (cm ³)		231.59	17.50		213.75	19.25	0.014	0.96
Total cortical volume (cm ³)		531.28	39.69		513.30	41.74	0.243	0.44
LH cortical volume (cm ³)		265.75	19.24		256.89	21.48	0.252	0.43
RH cortical volume (cm ³)		265.52	20.75		256.41	20.48	0.240	0.44
Total surface area (cm ²)		183.94	13.10		172.13	15.20	0.034	0.82
LH surface area (cm ²)		91.63	6.71		86.02	7.98	0.051	0.75
RH surface area (cm ²)		92.31	6.47		86.12	7.29	0.022	0.89
Mean cortical thickness (mm)		2.579	0.082		2.652	0.078	0.019	0.91
LH mean cortical thickness (mm)		2.580	0.080		2.659	0.078	0.042	1.01
RH mean cortical thickness (mm)		2.579	0.087		2.645	0.081	0.011	0.79

Table 5. 2. Median, mean, and standard deviation (SD) of demographic variables and global brain morphometric variables (LH, left hemisphere; RH, right hemisphere). The global measurements of brain morphometry—intracranial volume, total grey matter volume (including cortex and basal ganglia), total cortex volume, total surface area, and whole brain mean thickness—were obtained with VBM8 and FreeSurfer. Significant *p*-values controlled by FDR correction ($q < 0.05$) and confidence intervals (95% CI) are shown in bold type.

5.3.3 Vertex-wise Analysis: Group Differences in Surface Area

Vertex-wise analysis of surface area revealed that the surface of the left and right frontal lobes was larger for math-gifted subjects, particularly in the left caudal and the right rostral middle frontal gyri, which are included in the dorsolateral prefrontal cortex. Moreover, the surface area of the left lateral occipital and inferior parietal lobes and of the right lingual gyrus was significantly larger in math-gifted subjects (**Table 5. 2**). The Cohen's *d* map indicates that the area of the bilateral parahippocampal gyrus, right mPFC and left anterior cingulate cortex is significantly larger in math-gifted subjects (**Figure 5. 1**). The inclusion of covariates such as sex, age, IQ, and total cortical volume does not noticeably alter the findings for cortical thickness or surface area (see Appendix Chapter 5).

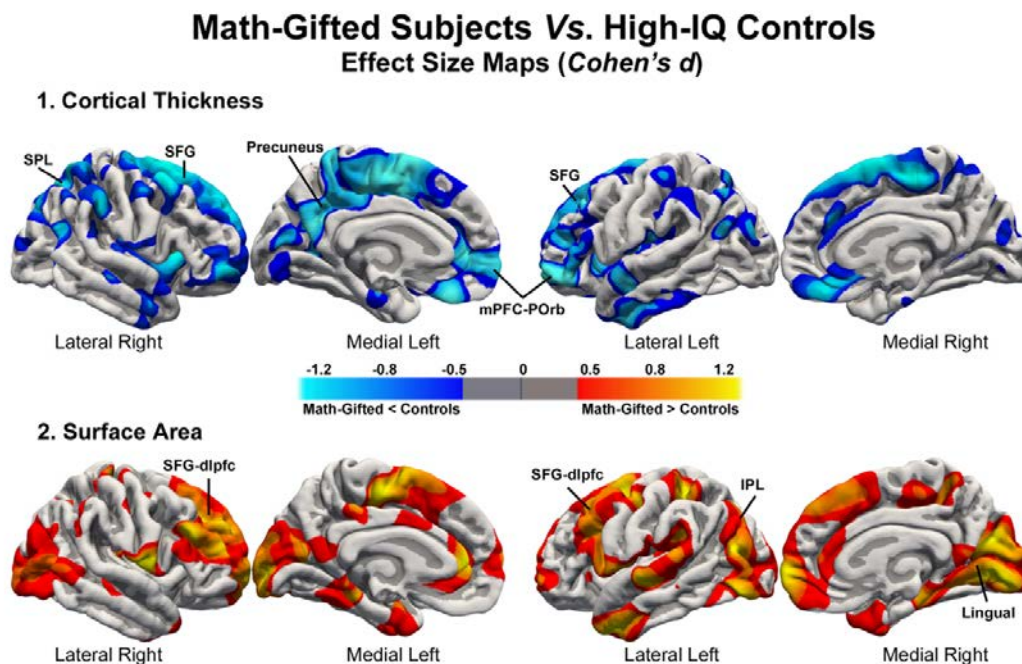


Figure 5. 1. Vertex-wise analysis. Group differences in (1) cortical thickness and (2) surface area. Thinner cortex in math-gifted adolescents is represented in blue, and larger surface area than high-IQ controls appears in warm colors. Math-gifted subjects did not present regions with significantly thicker cortex or lower surface area than controls. The Cohen's *d* maps are thresholded at $d > 0.5$ (medium effect, represented with dark blue or red), and $d > 0.8$ (high effect, represented in light blue or yellow). The clusters that survived the multiple comparisons correction ($CWP < 0.05$) were identified as SFG (superior frontal gyrus), SFG-dlpfc (superior frontal gyrus-dorsolateral prefrontal cortex), SPL (superior parietal lobule), IPL (inferior parietal lobule), mPFC-POrb (medial prefrontal cortex-pars orbitalis), and lingual.

5.4 Discussion

The relationship between cortical morphometry and intellectual abilities such as general intelligence or creativity has been widely described in the literature; however, to our knowledge, the relationship between cortical morphometry and math-giftedness has not been explored. The aim of this study was to explore potential morphometric differences, in particular cortical thickness and surface area, between math-gifted adolescents and controls using surface-based methodologies. A significantly thinner cortex accompanied by a larger surface area suggests that the cognitive precocity of math-gifted subjects could be associated with by above-age development of brain morphometry. We found that the cortex was thinner in the superior dorsolateral prefrontal and superior parietal regions and that the surface area was larger in the superior and middle dorsolateral prefrontal cortex, which are key regions of the fronto-parietal executive network. We also found the cortex to be thinner in the mPFC and precuneus and the surface area to be larger in the medial temporal lobes and the right mPFC, which are key nodes of the DMN. Therefore, our results support the initial hypothesis regarding the possibility of above-age brain maturation, not only of the fronto-parietal executive networks, but also of the DMN.

5.4.1 Neural Development in Math-giftedness

One of the main features that characterize gifted individuals is that they perform above their age in cognitive tests (mainly IQ) and creativity measurements, thus demonstrating a higher level of cognitive maturation than their same-age peers (Gross 2004; Geake 2008). Our findings of a thinner cortex and larger surface than in same-age controls suggest that this cognitive precocity may be the outcome of above-age neural development.

It is well known that dynamic reconfiguration during neurodevelopment entails synaptic pruning, myelination, and surface expansion. Several studies have suggested the existence of cortical thinning due to synaptic pruning (Changeux and Danchin 1976; Huttenlocher and Dabholkar 1997; Paus 2005; Petanjek et al. 2011) and neuropil myelination (Sowell et al. 2004; Gogtay and Thompson 2010) during adolescence. Furthermore, some cross-sectional studies also suggested that a thinner cortex at a given age might reflect earlier cortical maturation (Tamnes et al. 2010a; Tamnes et al. 2011). According to these data, our finding of decreased whole-brain cortical thickness in gifted

individuals could indicate a more mature brain in terms of synaptic pruning and myelination. In further support of earlier development in gifted individuals, our data also indicate that math-gifted adolescents show larger surface area and white matter volume. According to the “*Balloon Model*” hypothesis (Seldon 2005), this finding may reflect a more advanced level of myelination.

Therefore, we can speculate that the exceptional cognitive skills of math-gifted subjects might be linked to above-age neural development, as reflected by thinner cortex and highly expanded surface area. Nevertheless, future longitudinal studies are warranted to characterize the development of the brain in this group of cognitively talented individuals.

5.4.2 Between-Group Differences in Cortical Morphometry: Fronto-Parietal and Default Mode Networks

According to our findings, morphometric differences are localized in regions belonging to fronto-parietal and default mode networks, both of which are considered high-order cognitive systems that are subject to protracted development. The maturation of these networks during childhood and adulthood underlies the development of higher-level cognitive functions, such as executive functioning and creative thinking, which seem to be exceptional in gifted individuals (de Bie et al. 2012; Hoff et al. 2013).

The fronto-parietal network plays a key role in intelligence as seems to be is critical for executive control by keeping on-line working memory representations necessary for problem solving, decision-making, and other goal-directed processes (Baddeley 2003), (Jung and Haier 2007). Our findings complement previous data showing special characteristics of the fronto-parietal executive network (FPN) in terms of functionality (O'Boyle M. W. et al. 2005; Lee et al. 2006; O'Boyle Michael W. 2008; Prescott et al. 2010; Desco et al. 2011; Hoppe et al. 2012) and anatomical connectivity (Navas-Sanchez et al. 2014).

Therefore, our morphometric data, together with data from the above-mentioned reports, suggest that the special cortical characteristics of the fronto-parietal network might underlie high-level cognition with improved visuospatial working memory, mathematical skills, and executive capabilities.

Although the FPN has been extensively related to individual differences in general intelligence (Jung and Haier 2007), it is very unlikely that the implication of the FPN in giftedness could be explained merely in terms of IQ level, since the control group was matched for IQ.

According to theoretical definitions of giftedness, gifted individuals show not only higher IQ and enhanced executive functioning, but also exceptional creativity and higher task motivation (Renzulli 1978; Kießwetter 1985; Renzulli 1998; Heller et al. 2000; Kalbfleisch 2004; Sternberg and Davidson 2005). In recent years, an increasing number of functional and structural neuroimaging studies point to the implication of the DMN in creative thinking (Takeuchi et al. 2011a; Ellamil et al. 2012; Gonen-Yaacovi et al. 2013; Jung et al. 2013; Benedek et al. 2014; Wei et al. 2014). Consistently, our findings suggest that giftedness is associated with atypical cortical characteristics in regions of the DMN. In particular, we found that math-gifted subjects present thinner cortex in the precuneus and the mPFC, as well as larger surface area in the medial temporal lobes bilaterally (including the parahippocampal gyrus) and the right mPFC, areas that have been directly associated with creative thinking (Jung et al. 2013). Notwithstanding, some authors suggest that creativity does not rely exclusively on the DMN, but also on the interplay between DMN regions and other areas such as the dorsolateral prefrontal cortex, the inferior parietal cortex, and the orbitofrontal cortex (Aydin et al. 2007; Jung et al. 2010; Takeuchi et al. 2010; Shamay-Tsoory et al. 2011; Takeuchi et al. 2011b), which we also found to be atypical in our sample of gifted subjects.

We believe that our findings of atypical morphometry in regions of the fronto-parietal and default mode networks in math-gifted subjects could plausibly account for the existence of a neural substrate for exceptional executive functioning and creative thinking.

Additionally, we found surface area to be higher in the bilateral visual cortex of math-gifted subjects than in that of controls. The visual cortex has been extensively implicated in attentional functions as well as in visual imagery and visuospatial processing (Jehee et al. 2011; Leshikar et al. 2012; Moradi et al. 2012). fMRI reports in math-gifted subjects have shown activations in visual areas while performing executive functioning and fluid reasoning tasks (Desco et al. 2011); (O'Boyle M. W. et al. 2005; Lee et al. 2006). Likewise, in our previous DTI study, we also found that math-gifted subjects have a higher fractional anisotropy (FA) in the parieto-occipital and fronto-occipital tracts, thus

suggesting greater abilities in visuospatial stream processing (Navas-Sanchez et al. 2014). The implication of the occipital cortex in math-giftedness could be related to subjects' greater ability to produce enriched mental images associated with visuospatial working memory.

Finally, we believe that the integration of morphological, functional, and DTI data from math-gifted individuals will likely enhance our understanding of their special giftedness. We previously characterized the current math-gifted sample in terms of functionality—while performing executive functioning and fluid reasoning tasks (Desco et al. 2011)—and structural connectivity (Navas-Sanchez et al. 2014). In the present study, we describe morphometric features.

According to our findings, math-gifted subjects show greater bilateral activation in dorsal attentional and FPN networks (Desco et al. 2011), enhanced structural connectivity between fronto-parietal and fronto-striatal major tracts (Navas-Sanchez et al. 2014), and larger surface area accompanied by thinner cortex in fronto-parietal regions.

Previous studies in typical developing adolescents have explored the association between cortical morphometry, neural activity, and microstructural white matter organization. Studies on morphometric and functional features suggest the presence of a negative relationship between cortical thickness and functional activity (Lu et al. 2009; Nunez et al. 2011). Although the neural mechanisms underlying this negative association are unknown, it has been suggested that the synaptic pruning leading to cortical thinning during adolescence could also increase the selectivity and effectiveness of the neural structure, thus producing stronger functional activations (Lu 2009, Nunez 2011). Furthermore, Lu and colleagues (2009) proposed that skill level, such as that observed in math-gifted individuals, is associated with protracted development of functional activation in the brain, at least in fronto-parietal and attentional networks.

In addition to the thinner cortex in the dorsal stream of the FPN, we found greater cortical surface area in the dorsolateral prefrontal cortex bilaterally, thus suggesting the existence of above-age cortical properties in the FPN, which could underlie the greater and presumably protracted, fronto-parietal activation observed in the math-gifted adolescents we studied. This greater fronto-parietal activation, which was due mainly to greater functional bilateralism, could also be related to the enhanced organization of the white matter in the corpus callosum detected in our DTI study (Navas-Sanchez et al. 2014).

White matter microstructure and cortical properties are also negatively associated with maturational processes (Giorgio et al. 2008; Tamnes et al. 2010a). It has been proposed that age-related changes in cortical thickness and white matter microstructure may be driven, in part, by a common biological mechanism, presumed to be associated with changes in cerebral myelination (Kochunov et al. 2011). The combination of a thinner cortex and enhanced white matter organization could lead to a different pattern of activation during fluid reasoning and executive functioning tasks, thus facilitating the information processing that is crucial for higher intellectual capabilities. Math-gifted subjects are qualitatively and quantitatively different, not only in terms of brain activation and white matter organization, but also in terms of cortical morphometry. From a transversal imaging perspective, our studies depict a math-gifted brain characterized by exceptional and above-age properties in the fronto-parietal circuit.

Our study presents a series of limitations. First, the cross-sectional design prevents us from assessing the cognitive and neural maturation of the subjects. Of note, the term “precocity”, as used in this manuscript, refers merely to the presence of cognitive and neural features that correspond to those observed in older subjects. Furthermore, the sample size is relatively small. It is difficult to recruit larger samples, since we are studying an exceptional form of intelligence that is extremely rare in the population. However, our sample was very carefully selected, in that it comprised math-gifted adolescents and non-gifted controls with balanced gender effects who were of the same age and, importantly, within an approximately similar IQ range.

Our findings are also limited by the cognitive characterization of the two groups. Recruitment of math-gifted subjects was based on their admission to the ESTALMAT program, although controls were not evaluated and excluded by the same ESTALMAT program. Therefore, we cannot rule out the possibility that a control would have met the criteria for math-giftedness. However, given the low proportion of math-gifted subjects in the population, we can realistically assume that our controls were not gifted.

Most importantly, the effect of possible misclassification of controls weakens our hypothesis, since the statistical effect of giftedness would appear diminished. Nevertheless, our findings remain reasonably robust despite this potential drawback.

5.5 Conclusions

In summary, math-gifted adolescents showed special morphological properties in regions of the fronto-parietal and default mode networks in charge of executive processing and creative thinking, respectively. The combination of reduced cortical thickness and larger surface area in these regions suggests the presence of above-age neural maturation in gifted individuals.

5.6 References

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Appendix Chapter 5

In this appendix, we show the clusters obtained from the CWP correction, and the Cohen's d maps thresholded to $d > 0.8$ (large effect size). We also intend to demonstrate that IQ and gender have minimal effect on cortical morphometry analyses.

Figure 5.A1. Effect-size maps (thresholded to Cohen's $d > 0.8$) and clusters obtained from the CWP < 0.05 for cortical thickness and surface area analyses.

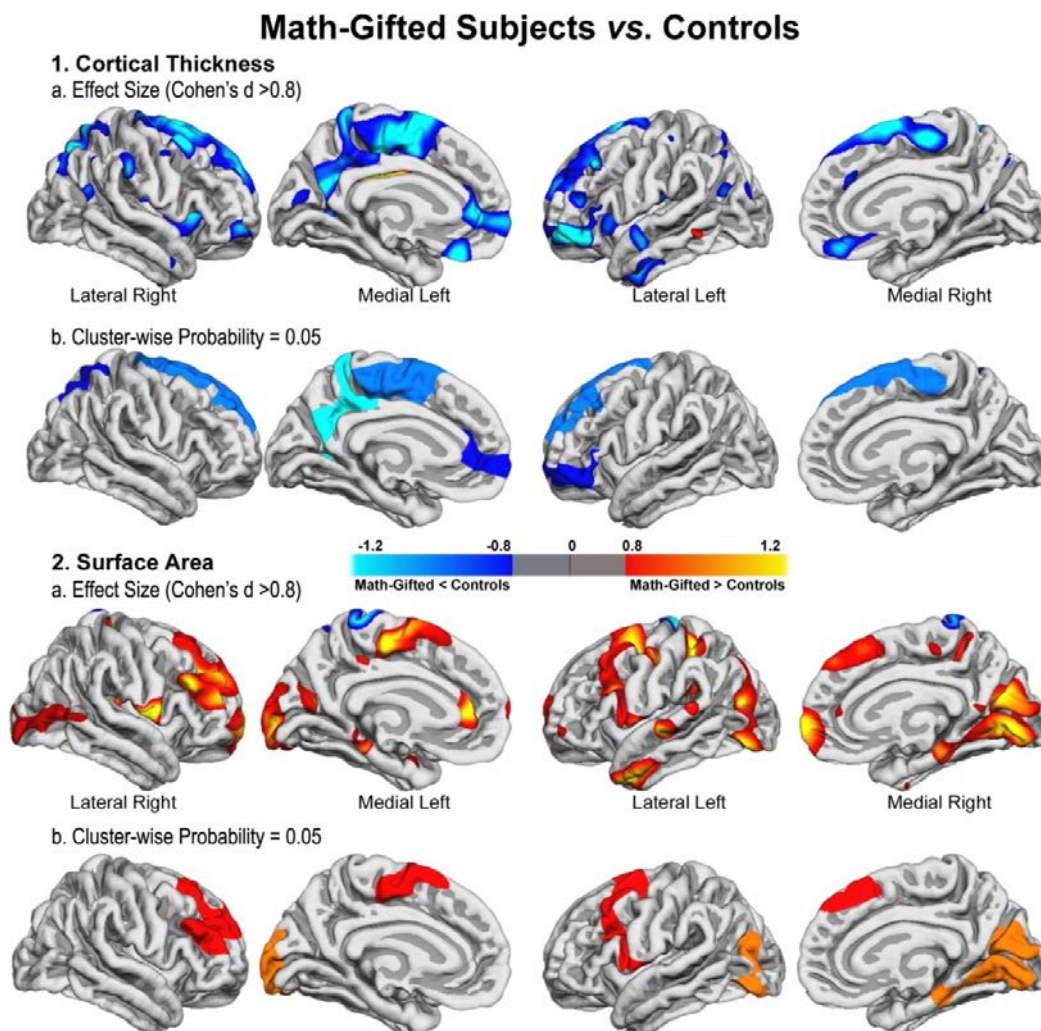


Figure 5.A2. The effect size maps of the vertex-wise analyses of cortical thickness are similar between different statistical models (*t* test; ANCOVA controlling for total cortical volume; ANCOVA controlling for gender and IQ).

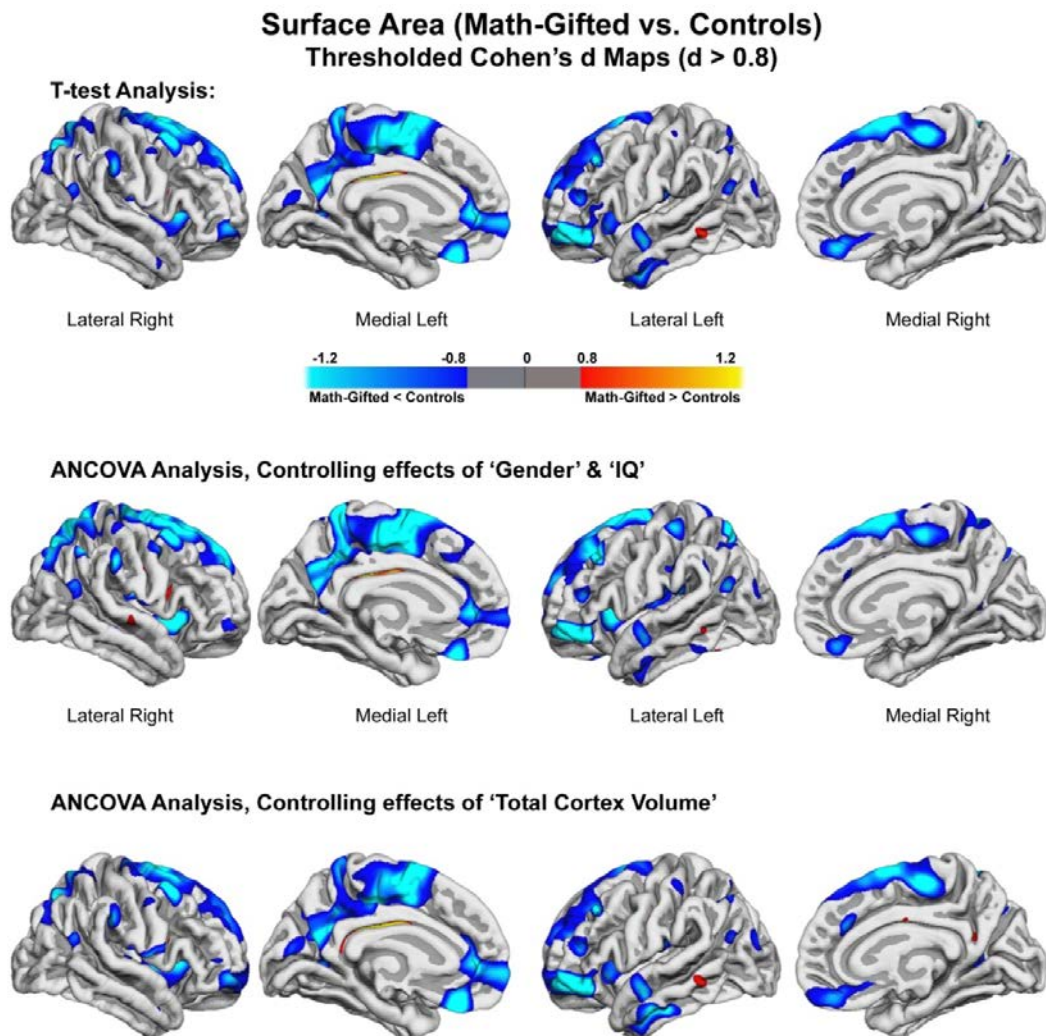
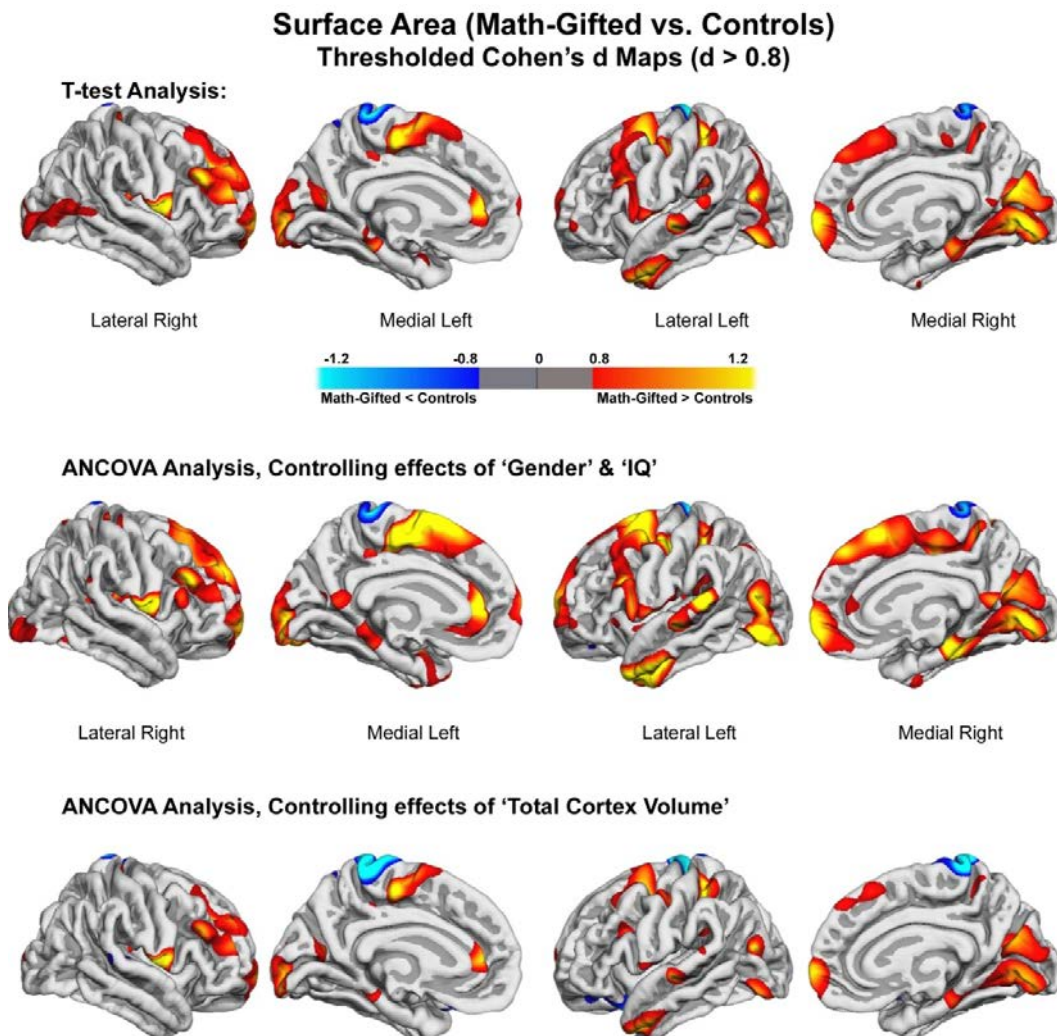


Figure 5.A3. Effect size maps of the vertex-wise analyses of surface area are similar between different statistical models (*t* test; ANCOVA controlling for total cortex volume; ANCOVA controlling for gender and IQ).



Chapter 6. General Discussion and Conclusions

General Discussion

This final chapter of the thesis summarizes the main findings and presents the general conclusions of this work.

The aim of this PhD-thesis was to describe the neural basis of math-giftedness assessing functional activations (**chapter 3**), white matter microstructure (**chapter 4**) and cortical morphometry (**chapter 5**). In order to do that, we recruited 13 math-gifted adolescents previously selected by the ESTALMAT program (a national program focused on math-giftedness). Controls, from the same region, were group-matched by age with the math-gifted group. All the enrolled subjects had to pass an IQ test and a neuroimaging study in the same session. The neuroimaging study was composed by the acquisition of a task-based functional MRI, a Diffusion Tensor Imaging and a T1-Weighted structural MRI. These three neuroimaging techniques allow us to present how is the brain functioning during working memory and fluid reasoning tasks as well as the structure of the gray and white matter. Moreover, we used the IQ score in the statistical analyses in order to adjust for the variance explained by general intelligence and ensure that the observed effect belongs strictly to math-giftedness. The whole study thus complete a global view of the brain characteristics in math-gifted individuals during adolescence.

Considering our results all together it is remarkable that math-gifted subjects present special brain characteristics, not only restricted to a neural functionality, but also in white matter microstructure and cortical features. Math-gifted subjects present different neural features in key regions of the fronto-parietal network, as well as in the axon bundles that interconnect regions within the network. According to previous neuroimaging studies focused on math-giftedness, these type of intelligence showed a distinctive functional pattern of bilateral activations in the frontoparietal network. (O'Boyle M. W. et al. 2005; Lee et al. 2006; O'Boyle Michael W. 2008; Prescott et al. 2010; Hoppe et al. 2012). Individual differences in the structure and function of the fronto-parietal executive network are meaningfully related to variability in human intelligence (Jung and Haier, 2007). Furthermore, the enhanced bilateralism observed in math-gifted adolescents is supported by heightened white-matter microstructure in corpus callosum, as previously hypothesized Singh and O'Boyle (Singh and O'Boyle, 2004).

Furthermore, in coherence with the hypothesis of this thesis, the cognitive behavior of math-giftedness entails not only special functional characteristics, but also greater

structural connectivity and cortical features non-dependent of the IQ. Moreover, these differences could affect specific structures of the frontoparietal executive network and other key regions related with information processing. Reading our results will probably raise some questions about the relationship between the measurements obtained from the three MRI modalities and also their relationship with math-giftedness. The Figure 6.1 summarizes the main results of this thesis in an attempt to facilitate the global interpretation of the regions involved in math-giftedness. The brain characteristics in math-gifted subjects would be the basis for overperforming average subjects in terms of intelligence and creativity, according to the functions related with the fronto-parietal and default mode networks.

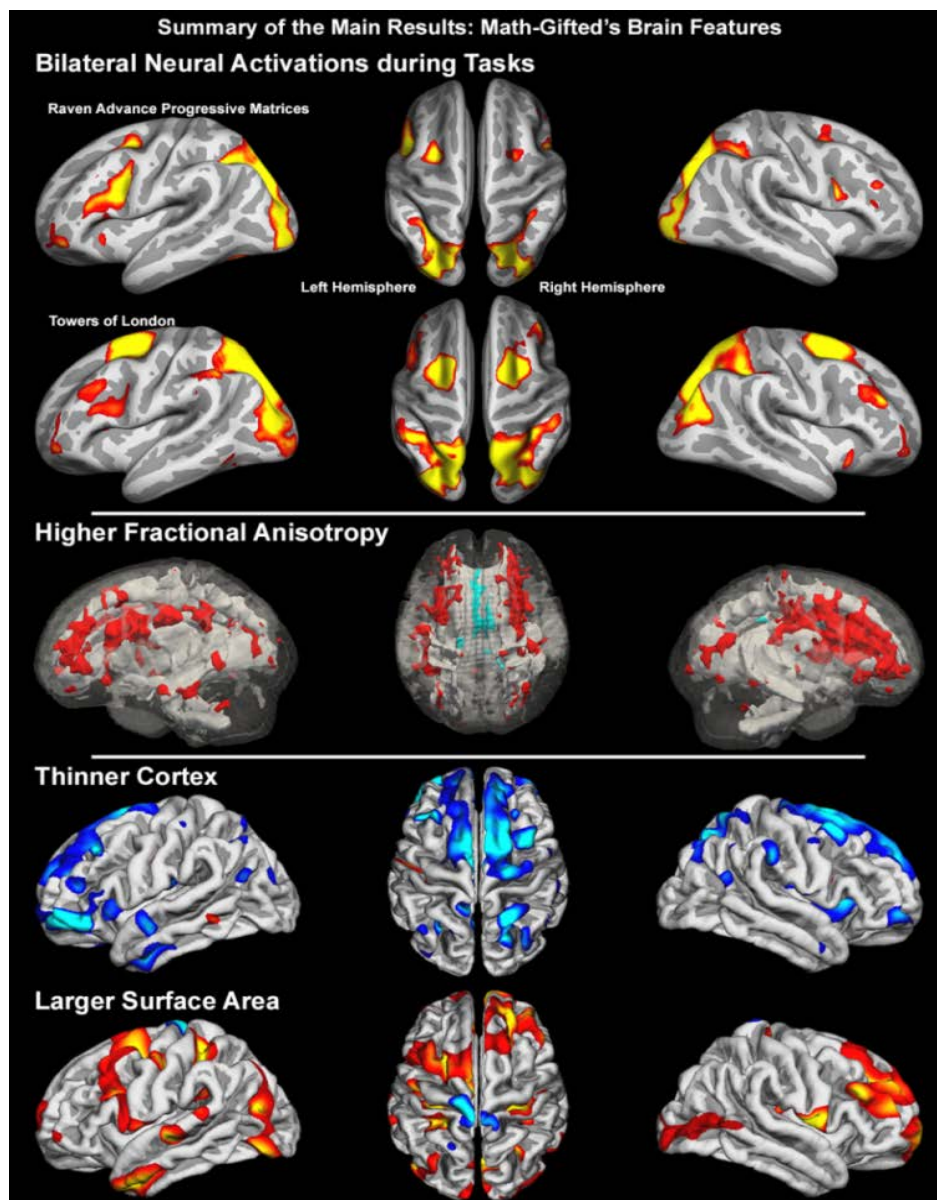


Figure 6. 1. Summary of the main results of this Thesis.

Firstly, a pattern of increased activation in fronto-parietal regions may be positively correlated with an enhanced white matter microstructure, as some authors previously reported (Bunge 2007). This relationship could be explained by developmental changes such as synaptic pruning, myelination and increased strength of connections within or between brain regions.

In the same way, previous neuroimaging studies pointed out that the relationship between microstructural white-matter and grey matter properties (cortical thickness and volume) is negative, because of neurobiological age-related processes of maturation (Tamnes 2011; Giorgio 2008). These age-related changes in cortical thickness and white matter organization are driven, in part, by a common biological mechanism, presumed to be related to changes in cerebral myelination (Kochunov et al. 2011). The myelination into the periphery of the cortical neuropil, and the selective synaptic pruning during adolescence, together with the enhanced white matter organization in fronto-parietal regions could explain that math-gifted adolescents showed above-age maturation.

Finally, the relationship between cortical thickness and activation could also be explained by neurodevelopmental processes. The adolescence is a critical period in brain development. During this stage, different neurophysiological processes produce sharpened changes in the brain, when both morphology and function are changing. Morphometrically it is well described that there is a cortical thinning and areal expansion. Both cortical thickness and surface area measurements give us information about different biological developmental factors. Cortical surface area is driven by the number of cortical columns, whereas thickness is influenced by the number of cells (neurons and glia) within a column (Rakic 1988, 1995, 2007). Increasing surface area, gifted subjects acquires heightened brain structure in frontal regions that are crucial for high-order cognitive functions. The largest area of some cortical regions could be related with the extensive pattern of activations showed by math-gifted subjects; however previous neuroimaging studies described the significant negative correlation between cortical thickness and neural activations, not only in typically developing adolescents (Lu 2009; Nunez, 2011) but also in non-typically developing subjects, such as early blind subjects (Anurova et al. 2014). Then, the synaptic pruning suffered by the brain cortex could lead to cortical thinning and, together with other neurophysiological processes, could increase selectivity and effectiveness of the neural structure, leading stronger activations. Lu and colleagues (2009) proposed that skill-levels, such as math-giftedness might be, are

associated with functional development at least in fronto-parietal and attentional networks, and activation could correspond to above-age cortical morphology in these regions.

In summary, the above-their-age structural brain features could lead to a special pattern of activations in math-gifted subjects. The cortical thinning and the greater white matter organization could underlie the wider pattern of activations during fluid reasoning and executive functioning tasks, facilitating processing information that is crucial for higher intellectual capabilities and for creativity. In math-giftedness, the combination of these neural characteristics could be the core of a gifted behavior.

This thesis presents original contributions in the field of neuroscience of intelligence. Firstly, the broad description of the brain features of math-giftedness contribute to fulfill the neural basis of math-giftedness. The novelty of the DTI and cortical morphometry data in math-gifted subjects add new insight into the field. Nevertheless, one of the most important things is that, rejecting the conception of math-giftedness as an extremely intelligent people, we obtain certain results supporting the psychological models that include creativity and task-commitment (Renzulli, 1978; Kiesswetter, 1985, Gagné, 1985; Heller, 1994).

Conclusions

The brain characteristics that underlie math-giftedness were studied using different neuroimaging methodologies: task-related fMRI; diffusion tensor imaging, and cortical morphometry analyses.

The specific conclusions reached in this thesis are:

1. Regarding the neural substrates of fluid reasoning and visuospatial working memory in adolescents with mathematical giftedness as compared with age-matched controls.

1.1 Math-gifted group presented greater bilateralism of activations in the fronto-parietal network, which is probably associated with the higher capacity of math-gifted subjects to solve complex visuospatial and analytical tasks demanding logical thinking.

1.2 Task difficulty is related with the extended pattern of activations in math-gifted adolescents.

2. Regarding the relationship between math-giftedness and IQ with the white-matter microstructure in math-gifted adolescents and age-matched controls.

2.1 Structural connectivity (assessed with Fractional Anisotropy from Diffusion Tensor Imaging) between frontal and parietal regions in math-gifted subjects appeared enhanced as compared with aged-matched controls.

2.2 Math-giftedness correlated with white matter microstructure in fronto-parietal and frontostriatal association tracts whereas intelligence quotient correlates positively with white matter microstructure of the corpus callosum.

3. Regarding the cortical morphometry in math-gifted subjects as compared with controls group-matched in IQ and age.

3.1 Math-gifted adolescents showed thinner cortex and larger surface area in key regions of the fronto-parietal and default mode networks.

3.2 Math-gifted individuals showed an above-their-age cortical morphometry, resembling cortical features typically found in adults.

Possible Future Lines of Research

Several possible lines for future works, as well as many questions still remain open:

- Testing the developmental precocity hypothesis in math-gifted subjects. In order to test the hypothesis about the precocity in terms of brain maturation, a longitudinal study should be necessary, not only with cortical morphometry assessment but also assessing fractional anisotropy changes over time. Several neuroimaging studies have described the trajectory and the dynamics of cortical thickness, as well as the FA in the white matter, during childhood and adolescence, depending on the IQ. However, it has not been described the trajectory of these variables in math-gifted subjects.

- Testing the Default Mode Network in math-giftedness. In the last years, several neuroimaging studies focused on creativity using different tasks such as divergent thinking or fluid analogies tasks. Using similar tasks we could test the Default Mode Network functionality in these children.

- Discriminating math-giftedness. Integrate the information of brain characteristics in order to discriminate between math-giftedness and some other populations (highly IQ level subjects, highly creative subjects, etc.) crossing the fMRI, DTI and cortical morphometry data. This analyses could contribute to better define the most important features of the gifted brain.

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